1. Phylogeny  
   Tyrosine‐protein kinase Yes (YES1) belongs to the Src family kinases (SFKs), a well‐conserved paralog group of non‐receptor tyrosine kinases that emerged early in metazoan evolution. YES1 is evolutionarily related to classical SFK members such as Src, Fyn, and Lyn, sharing a highly conserved modular architecture that includes regulatory and catalytic domains. It is present in a wide variety of metazoan species with orthologs detected from invertebrates to mammals, underscoring its essential role in eukaryotic cell signaling. The kinase belongs to the cytoplasmic group of protein tyrosine kinases and is phylogenetically distinct from receptor tyrosine kinases, which have evolved additional extracellular ligand‐binding domains. Comparative phylogenetic analyses indicate that YES1 and its close relatives have maintained a high degree of sequence conservation across vertebrates, suggesting that the regulatory mechanisms and substrate specificities typical of SFKs were established in the Last Eukaryotic Common Ancestor (LECA) or shortly thereafter (berndt2021newstructuralperspectives pages 1-2, gocek2014nonreceptorproteintyrosine pages 1-2, santos2016paralogspecificpatternsof pages 19-20).
2. Reaction Catalyzed  
   YES1 catalyzes the transfer of the γ‐phosphate from ATP to the hydroxyl group of tyrosine residues on protein substrates. The reaction mechanism follows the classic bi–bi kinetic model observed in protein kinases where ATP binds to the kinase active site in the presence of a divalent metal ion, and the phosphoryl group is transferred to the phenolic hydroxyl of a tyrosine residue, yielding ADP and a phosphotyrosine-modified substrate. This phosphorylation event plays a critical role in modulating substrate protein activity, stability, and interaction with downstream signaling molecules. YES1 thus serves as a molecular switch by converting external receptor stimulation (via receptor tyrosine kinases such as EGFR, PDGFR, CSF1R, and FGFR) into a phosphorylation cascade that influences various cellular processes (berndt2021newstructuralperspectives pages 1-2, bhullar2018kinasetargetedcancertherapies pages 13-13).
3. Cofactor Requirements  
   As with most protein kinases, YES1 requires divalent metal ions, particularly Mg²⁺, which coordinate with ATP to facilitate efficient phosphoryl transfer. The presence of Mg²⁺ helps to stabilize the negative charges on the phosphate groups of ATP, positioning it correctly within the catalytic pocket of the kinase to allow the transfer of the phosphate group onto the substrate’s tyrosine residue. Although there is no specific evidence in the provided reports that YES1 requires additional unique cofactors, the conserved catalytic mechanism across the Src family suggests that Mg²⁺ serves as an essential cofactor for YES1 activity (berndt2021newstructuralperspectives pages 1-2, santos2016paralogspecificpatternsof pages 19-20).
4. Substrate Specificity  
   YES1 exhibits substrate specificity characteristic of Src family kinases. It phosphorylates a variety of physiological substrates that are critical for cellular processes such as junction assembly, cell migration, and cell cycle regulation. Physiologically, YES1 is known to phosphorylate:  
   • PARD3 – upon activation of EGFR, YES1 phosphorylates this polarity-related protein to promote the assembly of epithelial tight junctions.  
   • CTNND1 – through stimulation of related kinases such as Fyn and FER, YES1 indirectly modulates the phosphorylation state of junctional components to influence cell–cell adhesion.  
   • DPYSL2 (also known as CRMP2) – in T-cells, CXCL12 stimulation results in the phosphorylation of this substrate, thereby promoting cell migration.  
   • CDK4 – YES1 phosphorylates cyclin-dependent kinase 4, thus regulating the progression of the G₁ phase of the cell cycle, and it is also implicated in G₂/M progression and cytokinesis.  
   • OCT2 – by phosphorylating the organic cation transporter OCT2, YES1 can enhance its transport function.

Moreover, motif analyses derived from yeast-based phosphorylation assays indicate that YES1, similar to other SFKs, exhibits enrichment for specific amino acid residues flanking the phosphotyrosine site. For instance, the presence of negatively charged residues at specific positions relative to the tyrosine appears to be a determinant for recognition by YES1, although a fully defined consensus sequence for YES1 remains less clearly delineated compared with some other kinases (bhullar2018kinasetargetedcancertherapies pages 13-13, corwin2016decipheringhumancytoplasmic pages 126-130, santos2016paralogspecificpatternsof pages 19-20).

1. Structure  
   YES1 is characterized by a modular organization typical of Src family kinases. Its structure can be divided into several domains with distinct functions:  
   • An N-terminal SH4 domain – contains sites for myristoylation (and in some cases palmitoylation) that mediate membrane anchoring, ensuring correct subcellular localization upon activation.  
   • A unique region – this segment provides an additional layer of regulatory control, which may contribute to isoform-specific functional differences.  
   • SH3 domain – facilitates protein–protein interactions by binding proline-rich motifs in partner proteins, an interaction that is important for both substrate recognition and intramolecular regulation.  
   • SH2 domain – recognizes and binds to phosphotyrosine-containing sequences on activated receptors and other signaling proteins, thus playing a central role in propagating downstream signaling events.  
   • Catalytic kinase domain (SH1) – contains the active site responsible for ATP binding and phosphoryl transfer, exhibiting the conserved kinase fold and key catalytic residues analogous to those in other SFKs.

Crystal structures of related Src kinases reveal that the active site of YES1 is highly conserved and contains regulatory phosphorylation sites, such as an activation loop whose phosphorylation correlates with increased catalytic activity, and an inhibitory C-terminal region that, when phosphorylated, binds intramolecularly to the SH2 domain to maintain an inactive conformation. Unique features of YES1 might include variations in the unique region that differentiate its substrate binding or regulatory interactions from other SFKs (berndt2021newstructuralperspectives pages 1-2, garmendia2022yes1anovel pages 1-2, gocek2014nonreceptorproteintyrosine pages 1-2).

1. Regulation  
   YES1 regulation is multifaceted and involves several post-translational modifications and protein-protein interactions. Key regulatory mechanisms include:  
   • Autophosphorylation – YES1 undergoes autophosphorylation on its activation loop, which promotes a conformational change to an active state. In contrast, phosphorylation at the C-terminal region by regulatory kinases (e.g., C-terminal Src kinase, CSK, in related systems) helps maintain an inactive conformation in other SFKs; while specific CSK interactions with YES1 have not been as extensively described, regulatory parallels in the Src family suggest similar mechanisms (berndt2021newstructuralperspectives pages 1-2, gocek2014nonreceptorproteintyrosine pages 2-3).  
   • Recruitment by RTKs – Upon stimulation of receptor tyrosine kinases such as EGFR, PDGFR, CSF1R, and FGFR, YES1 is recruited to phosphorylated receptors. This recruitment, mediated largely by the SH2 domain binding to phosphotyrosine motifs on activated receptors, facilitates its activation and targeting to specific substrates in the plasma membrane microdomains (berndt2021newstructuralperspectives pages 1-2, kook2024emergingrolesof pages 1-2).  
   • Interactions with adaptor proteins – The SH3 and SH2 domains mediate interactions with regulatory and adaptor proteins, enhancing the selectivity and spatial coordination of substrate phosphorylation. For example, YES1 phosphorylates components such as PARD3 and supports the activation of other kinases like Fyn and FER through such interactions, which further amplifies downstream signaling (garmendia2022yes1anovel pages 1-2, corwin2016decipheringhumancytoplasmic pages 146-149).

These regulatory modifications allow YES1 to function as a finely tuned signaling node. The dynamic interplay between activating autophosphorylation, receptor-mediated recruitment, and inhibitory intramolecular bonds ensures that YES1 activity is appropriately modulated in response to various extracellular stimuli (corwin2016decipheringhumancytoplasmic pages 152-155, kook2024emergingrolesof pages 13-14).

1. Function  
   YES1 plays a central role in integrating extracellular signals into cellular responses that regulate a broad range of biological processes. Its well-documented functions include:  
   • Regulation of cell growth and survival – YES1 phosphorylates key substrates involved in cell cycle progression, such as cyclin-dependent kinase 4 (CDK4), thereby regulating the G₁ phase and influencing subsequent stages of cell division, including roles in G₂/M progression and cytokinesis.  
   • Modulation of cell-cell adhesion and cytoskeleton remodeling – By phosphorylating junctional proteins such as PARD3 and indirectly modifying CTNND1 at cell-cell contacts via the activation of related kinases (Fyn and FER), YES1 contributes to the maintenance and dynamic remodeling of epithelial and other cell junctions.  
   • Facilitation of cell migration – YES1 phosphorylates the collapsin response mediator protein 2 (DPYSL2/CRMP2) in T-cells following CXCL12 stimulation, a modification that enhances cell motility. Additionally, YES1 participates in CD95L/FASLG signaling pathways that mediate AKT-dependent migration, linking its activity to immune cell trafficking as well as cancer cell invasiveness.  
   • Regulation of transporter activity – Through phosphorylation of the organic cation transporter OCT2, YES1 enhances transporter function, illustrating its role in modulating cellular uptake and metabolic processes.

These functions position YES1 as a critical regulator in oncogenic signaling networks. Its overexpression and amplification have been linked to various cancers, where aberrant YES1 activity contributes to uncontrolled proliferation, survival, and resistance to targeted therapies. Thus, YES1 is not only a central component of normal cellular signaling but also a potential therapeutic target in oncology (bhullar2018kinasetargetedcancertherapies pages 13-13, garmendia2022yes1anovel pages 1-1, kook2024emergingrolesof pages 1-2).

1. Other Comments  
   In addition to its core functions, YES1 has garnered significant attention in the context of cancer biology due to its amplification and overexpression in a variety of solid tumors. Notably, YES1 gene amplifications are correlated with poor prognosis and have been implicated in resistance to targeted therapy regimens involving EGFR and other receptor tyrosine kinase inhibitors. For example, overexpression of YES1 has been associated with resistance to EGFR-targeted drugs, and treatment with broad-spectrum SFK inhibitors such as dasatinib has shown some efficacy in overcoming this resistance. Recent studies also suggest that YES1 expression may serve as a predictive biomarker for response to such treatments, thereby identifying patients who might benefit from YES1-targeted strategies (garmendia2022yes1anovel pages 1-2, kook2024emergingrolesof pages 1-2, kook2024emergingrolesof pages 13-14).

Emerging proteomic studies have further indicated that YES1 exists in distinct proteoforms that may differentially respond to pharmacological interventions, adding another layer of complexity to its regulation and functional output (leo2023proteoformleveldeconvolutionreveals pages 6-8). Moreover, the potential for targeting unique regulatory elements within the YES1 structure – such as its intrinsically disordered N-terminal regulatory region – is an area of active research, with the promise of developing selective inhibitors that minimize off-target toxicity often observed with broader SFK inhibitors (chakraborty2019targetingdynamicatpbinding pages 9-10).

Disease associations extend beyond oncogenesis, as YES1 is involved in fundamental cellular processes such as T-cell migration and epithelial barrier formation, thereby implicating it in immune modulation and tissue integrity. Ongoing research aims to elucidate the full spectrum of YES1 substrates and signaling networks, which may lead to refined therapeutic approaches that target specific aspects of YES1-mediated signaling pathways (corwin2016decipheringhumancytoplasmic pages 146-149, kook2024emergingrolesof pages 13-14).

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