1. Phylogeny  
   YES1 is a non‐receptor protein tyrosine kinase that belongs to the Src family kinases (SFKs), an evolutionarily conserved group of enzymes present in all metazoans. Comparative analyses using human kinome data have shown that YES1 shares a high degree of sequence identity and a characteristic modular domain organization with other prominent SFK members such as Src, Fyn, and Lyn. Phylogenetic reconstructions indicate that the catalytic domain of YES1 clusters with these kinases, reflecting a common evolutionary origin from an ancestral Src family kinase that existed in early metazoans. This kinase is detected across diverse vertebrate lineages and even in invertebrates, confirming its ancient origin and the critical pressure to conserve its function throughout evolution. The evolutionary history of YES1 suggests that while subtle structural variations confer unique regulatory and substrate recognition properties, its overall domain architecture has been retained from the common ancestor of animals (Bradley2019EvolutionOfProtein pages 1-2, Garmendia2022YES1ANovel pages 1-2, Kook2024EmergingRolesOf pages 1-2).
2. Reaction Catalyzed  
   YES1 catalyzes the phosphorylation of tyrosine residues on substrate proteins, a hallmark reaction of protein tyrosine kinases. The biochemical reaction involves the transfer of a phosphate group from ATP to the hydroxyl group of an L-tyrosine residue, resulting in the formation of ADP, a phosphorylated protein, and the release of a proton. This reaction can be formally represented as:  
     ATP + [protein]-(L-tyrosine) → ADP + [protein]-(L-tyrosine phosphate) + H⁺.  
   This phosphoryl transfer is central to the function of YES1 in initiating and propagating intracellular signaling cascades that are critical for regulating cellular growth, survival, adhesion, and migration (Bradley2019EvolutionOfProtein pages 25-25, Sprowl2016APhosphotyrosineSwitch pages 10-10).
3. Cofactor Requirements  
   The catalytic activity of YES1, like that of most protein kinases, is strictly dependent on the presence of divalent metal ions. Specifically, Mg²⁺ ions serve as essential cofactors for YES1 activity by coordinating with the ATP molecule in the catalytic pocket. This coordination plays a vital role in properly orienting the γ-phosphate group of ATP for efficient transfer to the target tyrosine residue on the substrate. The reliance on Mg²⁺ is a conserved biochemical feature among protein kinases and is crucial for the stabilization of the substrate–ATP complex during the phosphoryl transfer reaction (Cann2017MeasuringKinaseActivity—a pages 37-44).
4. Substrate Specificity  
   YES1 exhibits substrate specificity that is characteristic of Src family kinases. Although there is no single, definitive consensus sequence exclusively associated with YES1 phosphorylation, studies on the human tyrosine kinome have demonstrated a preference for substrates that contain specific amino acid contexts favorable for tyrosine phosphorylation. Through its catalytic domain, YES1 phosphorylates key substrates in diverse cellular processes. For example, following the activation of receptor tyrosine kinases such as EGFR, YES1 phosphorylates PARD3; this phosphorylation event plays an important role in the assembly of epithelial tight junctions. In parallel, YES1 facilitates the phosphorylation of junctional proteins like CTNND1 indirectly by activating other Src family kinases such as FYN and FER at cell–cell contacts. In immune cell contexts, YES1 is involved in phosphorylating collapsin response mediator protein 2 (also designated DPYSL2) upon stimulation by chemokines like CXCL12, thereby promoting T-cell migration. YES1 also directly phosphorylates cyclin-dependent kinase 4 (CDK4), a critical regulator of the G1 phase of the cell cycle, and it catalyzes phosphorylation events that enhance the functional activity of organic cation transporter OCT2. The substrate-selected motifs appear to favor local sequence contexts that are conducive to binding by the SH2 domain, which recognizes phosphotyrosine residues, and the SH3 domain, which binds to proline-rich regions; however, a specific consensus motif for YES1 remains less well established compared to some serine/threonine kinases (Sprowl2016APhosphotyrosineSwitch pages 10-10, Kook2024EmergingRolesOf pages 2-4, Zhao2020ScribbleSubcellularLocalization pages 18-23).
5. Structure  
   YES1 displays the canonical structural organization observed for Src family kinases. At its extreme N-terminus, YES1 contains an SH4 domain that harbors the sequence motifs necessary for myristoylation and, in many cases, palmitoylation; these post-translational lipid modifications are critical for anchoring the protein to cellular membranes and for specifying its subcellular localization. Immediately following the SH4 domain is a unique region that is specific to YES1 and may contribute additional regulatory functions distinct from its paralogs. The protein then encompasses an SH3 domain, which is primarily responsible for binding to proline-rich motifs in interacting proteins and is also involved in intramolecular interactions that help maintain an autoinhibited state. Adjacent to the SH3 domain is an SH2 domain that functions to bind phosphotyrosine-containing sequences, thereby facilitating specific substrate recognition and the assembly of signaling complexes. The C-terminal region of YES1 contains the catalytic or kinase domain (often referred to as the SH1 domain). This catalytic domain is organized into a bilobed structure where the smaller N-terminal lobe is primarily responsible for binding ATP and the larger C-terminal lobe is involved in substrate binding. Within the kinase domain, several key structural features are present: the activation loop, which must be phosphorylated for full enzymatic activation; the C-helix, which positions critical catalytic residues; and a hydrophobic spine that is essential for stabilizing the active conformation of the enzyme. Advanced structural studies, including crystallography of related Src family members and computational modeling, support the modular and dynamic nature of YES1’s three-dimensional organization (Bludau2022TheStructuralContext pages 21-23, Kukenshoner2017SelectiveTargetingOf pages 30-35, Zhao2020ScribbleSubcellularLocalization pages 18-23).
6. Regulation  
   The activity of YES1 is governed by multiple regulatory mechanisms that include post-translational modifications and protein–protein interactions. A key event in the activation of YES1 is the autophosphorylation of a tyrosine residue located within its activation loop; this autophosphorylation induces a conformational shift that opens the catalytic cleft and enhances substrate access to the active site. In contrast, phosphorylation of a conserved tyrosine residue in the C-terminal tail—typically mediated by the C-terminal Src kinase (CSK)—results in an autoinhibited conformation. In this inhibited state, the SH2 domain binds intramolecularly to the phosphorylated tail, thereby occluding the active site and preventing substrate binding. In addition to phosphorylation, YES1 is subject to ubiquitination that can influence its protein stability and subcellular redistribution. Lipid modifications in the SH4 domain, specifically myristoylation and palmitoylation, also play essential roles in regulation by targeting YES1 to membrane microdomains where receptor tyrosine kinases (such as EGFR, PDGFR, CSF1R, and FGFR) reside. These membrane-localized interactions not only facilitate YES1 activation but also ensure that its catalytic activity is spatially coordinated with its downstream substrates (Kook2024EmergingRolesOf pages 13-14, Bhullar2018KinaseTargetedCancerTherapies pages 11-13).
7. Function  
   YES1 serves as a central regulator in various cellular processes as a non-receptor tyrosine kinase. It is broadly expressed in multiple tissue types, reflecting its fundamental role in both normal physiology and disease states. YES1 is primarily activated downstream of receptor tyrosine kinases. Upon activation of receptors such as EGFR, PDGFR, CSF1R, or FGFR, YES1 is recruited to the phosphorylated receptor complexes, where its kinase activity is triggered. One of the pivotal functions of YES1 is the phosphorylation of PARD3 in response to EGFR activation; such phosphorylation events facilitate the assembly of epithelial tight junctions, thereby contributing to the maintenance of cell–cell adhesion. In addition, YES1 indirectly promotes the phosphorylation of CTNND1 (catenin delta-1) through the stimulation of associated Src family members like FYN and FER at sites of cell–cell contact, further supporting the integrity of adherens junctions. YES1 also plays significant roles in immune cell function: following chemokine stimulation by CXCL12, YES1 phosphorylates collapsin response mediator protein 2 (DPYSL2), leading to enhanced T-cell migration. Beyond its involvement in adhesion and migration, YES1 phosphorylates cyclin-dependent kinase 4 (CDK4) to regulate the progression of the G1 phase of the cell cycle and is implicated in G2/M progression and cytokinesis. Furthermore, YES1 phosphorylates the organic cation transporter OCT2, leading to increased transporter activity, which may have implications in drug uptake and metabolic regulation. These diverse functions underscore YES1’s role in mediating key signaling pathways that regulate cell growth, survival, adhesion, migration, and division (Bludau2022TheStructuralContext pages 21-23, Kook2024EmergingRolesOf pages 2-4, Sprowl2016APhosphotyrosineSwitch pages 10-10, Wu2023YES1MediatedCUL9Phosphorylation pages 13-14, Bhullar2018KinaseTargetedCancerTherapies pages 13-13).
8. Other Comments  
   YES1 has been extensively evaluated as a potential druggable oncogene owing to its frequent overexpression and gene amplification in a variety of human cancers. Elevated YES1 expression correlates with enhanced tumor proliferation, increased metastatic potential, and resistance to conventional therapies. Broad-spectrum inhibitors, such as dasatinib, have been used experimentally to target YES1; however, these agents typically lack the specificity required to selectively inhibit YES1 without affecting other Src family kinases. Consequently, iterative compound screening approaches that incorporate advanced computational modeling and docking techniques have been employed to identify novel, more selective inhibitors of YES1. In several solid tumors—including non-small cell lung cancer, breast cancer, colorectal carcinoma, and gastric cancers—YES1 dysregulation has been implicated not only in tumor progression but also in acquired resistance mechanisms to therapies targeting EGFR and HER2. As a result, YES1 is both a prognostic biomarker and a promising therapeutic target in oncology. The development of selective inhibitors with improved potency and minimal off-target effects remains an active area of research, with the aim of effectively counteracting YES1-mediated drug resistance and tumor progression (Chiba2015IdentificationOfPotential pages 11-12, Kook2024EmergingRolesOf pages 13-14, Kukenshoner2017SelectiveTargetingOf pages 30-35, Bhullar2018KinaseTargetedCancerTherapies pages 11-13).
9. References  
   Bludau2022TheStructuralContext pages 21-23, Bradley2019EvolutionOfProtein pages 1-2, Bradley2019EvolutionOfProtein pages 25-25, Cann2017MeasuringKinaseActivity—a pages 37-44, Garmendia2022YES1ANovel pages 1-1, Garmendia2022YES1ANovel pages 1-2, Garmendia2022YES1ANovel pages 2-3, Garmendia2022YES1ANovel pages 3-4, Garmendia2022YES1ANovel pages 6-7, Garmendia2022YES1ANovel pages 8-8, Hamanaka2019YES1ISA pages 1-1, Hamanaka2019YES1ISA pages 1-2, Jin2022TyrosineProteinKinaseYES pages 1-2, Jin2022YESKinaseControls pages 1-5, Kook2024EmergingRolesOf pages 1-2, Kook2024EmergingRolesOf pages 13-14, Kook2024EmergingRolesOf pages 2-4, Kook2024EmergingRolesOf pages 4-6, Kook2024EmergingRolesOf pages 7-8, Kook2024EmergingRolesOf pages 8-10, Korademirnics2000SrcKinaseMediatedSignaling pages 2-3, Kukenshoner2017SelectiveTargetingOf pages 30-35, Simon…2015YesOncogenicActivity pages 1-2, Simon…2015YesOncogenicActivity pages 14-15, Sprowl2016APhosphotyrosineSwitch pages 10-10, Sprowl2016APhosphotyrosineSwitch pages 4-5, Uddin2021InfluenceOfYES1 pages 5-8, Wu2023YES1MediatedCUL9Phosphorylation pages 13-14, Yang2022BioactivePhytoconstituentsAS pages 1-2, Zhao2020ScribbleSubcellularLocalization pages 18-23, Zhao2020ScribbleSubcellularLocalization pages 98-100, Zhou2023RoleOfYES1 pages 1-4, Zhou2023RoleOfYES1 pages 5-7, Bhullar2018KinaseTargetedCancerTherapies pages 11-13, Bhullar2018KinaseTargetedCancerTherapies pages 13-13, Chiba2015IdentificationOfPotential pages 11-12