## Phylogeny

YES1 is classified within the Tyrosine Kinase (TK) group of the human kinome (manning2002evolutionofprotein pages 2-3, manning2002theproteinkinase pages 1-2). More specifically, it belongs to the Src family of non-receptor tyrosine kinases, which is part of the larger Src group (manning2002theproteinkinase pages 7-8, yaronbarir2024theintrinsicsubstrate pages 5-6). Other members of the Src family include SRC, FYN, FGR, LCK, HCK, LYN, and BLK (yaronbarir2024theintrinsicsubstrate pages 5-6, yaronbarir2024theintrinsicsubstrate pages 16-16). Phylogenetic analyses place YES1 in close relation to SRC and FYN, indicating significant sequence and functional homology (manning2002theproteinkinase pages 3-3, yaronbarir2024theintrinsicsubstrate pages 5-6). Orthologs of YES1 are conserved across vertebrates, including in rats and mice, and Src family kinases are specific to metazoans, with expansions in the human kinome compared to invertebrates like *C. elegans* and flies (ariki1997identificationofautophosphorylation pages 6-7, manning2002evolutionofprotein pages 1-2, yaronbarir2024theintrinsicsubstrate pages 2-2, yaronbarir2024theintrinsicsubstrate pages 6-7).

## Reaction Catalyzed

ATP + a protein-L-tyrosine = ADP + a protein-L-tyrosine phosphate

## Cofactor Requirements

YES1 kinase activity requires Mg2+ as a cofactor (garmendia2022yes1anovel pages 1-2, garmendia2022yes1anovel pages 9-9).

## Substrate Specificity

The intrinsic substrate specificity of YES1 is defined by preferences for certain amino acids flanking the central phosphorylated tyrosine (position 0) (yaronbarir2024theintrinsicsubstrate pages 16-16). The most critical positions for substrate recognition are from -1 to +3 (yaronbarir2024theintrinsicsubstrate pages 15-16). The consensus phosphorylation motif for YES1 shows a preference for acidic residues, such as glutamic acid (E) or aspartic acid (D), at positions -3 to -1 and/or +1 to +3 (yaronbarir2024theintrinsicsubstrate pages 16-16). It also favors hydrophobic residues at other flanking positions (yaronbarir2024theintrinsicsubstrate pages 16-16, ariki1997identificationofautophosphorylation pages 6-7). Specifically, YES1 favors Proline (P) and Glycine (G) at the -1 position (yaronbarir2024theintrinsicsubstrate pages 15-16). YES1 specificity is also influenced by priming phosphorylations, where the presence of a phospho-tyrosine (pY) or phospho-threonine (pT) in the substrate motif can modulate kinase activity (yaronbarir2024theintrinsicsubstrate pages 16-16).

## Structure

YES1 is a multi-domain protein characteristic of the Src family (clump2005cyesresponseto pages 1-2, garmendia2022yes1anovel pages 1-2). Its structure includes six functional domains: 1. The N-terminal SH4 domain, which contains signals for myristoylation and palmitoylation that anchor the kinase to the cell membrane (clump2005cyesresponseto pages 1-2, garmendia2022yes1anovel pages 1-2). 2. A unique domain, which varies among SFKs and provides docking sites that influence specificity (clump2005cyesresponseto pages 1-2, garmendia2022yes1anovel pages 1-2). 3. The SH3 domain, which binds to proline-rich sequences (clump2005cyesresponseto pages 1-2, garmendia2022yes1anovel pages 1-2). 4. The SH2 domain, which binds to phosphotyrosine-containing motifs (clump2005cyesresponseto pages 1-2, garmendia2022yes1anovel pages 1-2). 5. The SH1 domain, which is the catalytic kinase domain (clump2005cyesresponseto pages 1-2, garmendia2022yes1anovel pages 1-2). 6. A C-terminal regulatory region containing a key inhibitory tyrosine residue (clump2005cyesresponseto pages 1-2). The catalytic SH1 domain contains key regulatory features, including the activation loop and the C-helix, which are involved in conformational changes that control kinase activity (garmendia2022yes1anovel pages 1-1, clump2005cyesresponseto pages 2-3).

## Regulation

YES1 activity is tightly regulated by phosphorylation and intramolecular interactions (garmendia2022yes1anovel pages 1-1, clump2005cyesresponseto pages 1-2). In its inactive state, YES1 is autoinhibited through an intramolecular interaction where the C-terminal tail, phosphorylated on Tyr537 by C-terminal Src kinase (CSK), binds to its own SH2 domain, stabilizing a closed, repressed conformation (clump2005cyesresponseto pages 1-2, garmendia2022yes1anovel pages 1-1). Activation occurs when protein tyrosine phosphatases (PTPs) dephosphorylate Tyr537, which releases the SH2 domain and opens the kinase conformation (clump2005cyesresponseto pages 1-2, garmendia2022yes1anovel pages 2-3). Full activation involves the subsequent phosphorylation of a tyrosine residue within the activation loop, Tyr426 (analogous to Tyr416 in c-Src), which stabilizes the active conformation of the catalytic domain (clump2005cyesresponseto pages 1-2, garmendia2022yes1anovel pages 2-3). Rat c-Yes also undergoes autophosphorylation at a unique site, Tyr-32, in its N-terminal region (ariki1997identificationofautophosphorylation pages 6-7). Additionally, serine/threonine phosphorylations within the unique domain of YES1 regulate cell cycle progression (garmendia2022yes1anovel pages 2-3).

## Function

YES1 is a non-receptor tyrosine kinase expressed in tissues including hematopoietic lines, melanocytes, and germ cells, and is widely upregulated in many solid tumors (clump2005cyesresponseto pages 3-5, garmendia2022yes1anovel pages 3-4). It functions downstream of multiple upstream receptors, including receptor tyrosine kinases (RTKs) like EGFR, PDGFR, FGFR, and c-Kit, as well as G-protein coupled receptors (GPCRs) and cytokine receptors (clump2005cyesresponseto pages 3-5, garmendia2022yes1anovel pages 1-2). YES1 regulates key cellular processes including proliferation, survival, adhesion, migration, and differentiation (clump2005cyesresponseto pages 3-5, unknownauthors2015yesoncogenicactivity pages 1-2). It achieves this by activating multiple signaling pathways such as the PI3K/AKT, MAPK, and Wnt/β-catenin pathways (garmendia2022yes1anovel pages 3-4, clump2005cyesresponseto pages 3-5). Known downstream substrates and interacting partners of YES1 include the transcriptional coactivator YAP1 (phosphorylated at Y357), ANXA2, FAK (phosphorylated at Y861), the CD95 receptor, SHC, SHP2, and PI3K (garmendia2022yes1anovel pages 3-4, clump2005cyesresponseto pages 3-5, unknownauthors2015yesoncogenicactivity pages 1-2).

## Inhibitors

As a member of the Src family kinases, YES1 is targeted by broad-spectrum SFK inhibitors, including the clinically approved drugs dasatinib, saracatinib, and bosutinib (garmendia2022yes1anovel pages 1-1). The experimental inhibitor PP1 also targets Src family kinases (clump2005cyesresponseto pages 3-5). Novel small-molecule inhibitors with higher specificity for YES1 have been developed and show potent antitumor effects in preclinical models (garmendia2022yes1anovel pages 1-1, garmendia2022yes1anovel pages 1-2).

## Other Comments

YES1 is implicated in the progression, oncogenesis, and metastasis of multiple cancers, including colorectal, breast, lung, pancreatic, prostate, and liver cancers, as well as melanoma and glioma (garmendia2022yes1anovel pages 3-4). Upregulation of YES1 in tumors frequently occurs via gene amplification or an increase in gene copy number (garmendia2022yes1anovel pages 3-4, hamanaka2019yes1isa pages 1-2). YES1 amplification has been identified as a key mechanism of acquired resistance to targeted therapies against EGFR and HER2 (garmendia2022yes1anovel pages 1-1, hamanaka2019yes1isa pages 1-2). High YES1 expression often correlates with poor prognosis in cancer patients (garmendia2022yes1anovel pages 1-1).

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