## Phylogeny

YES1 is an evolutionarily ancient non-receptor tyrosine kinase of the Src family kinases (SFKs). Sequence comparison and phylogenetic reconstructions place its catalytic domain in the same clade as Src, Fyn and Lyn, reflecting divergence from an ancestral SFK present in early metazoans. Conservation extends from invertebrates to all vertebrate lineages, with only minor structural variations conferring paralogue-specific regulation and substrate recognition (Bradley et al., 2019; Garmendia et al., 2022; Kook et al., 2024).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine ⇌ ADP + H⁺ + [protein]-L-tyrosine-phosphate (Sprowl et al., 2016; Bradley et al., 2019).

## Cofactor Requirements

Mg²⁺ is essential for ATP coordination and catalytic activity (Cann, 2017).

## Substrate Specificity

Like other SFKs, YES1 prefers substrates that present tyrosine residues within sequence contexts compatible with SH2 (phosphotyrosine-binding) and SH3 (proline-rich) interactions, although a strict consensus motif is not defined. Documented targets include PARD3, CTNND1 (via FYN/FER), DPYSL2, CDK4 and the organic cation transporter OCT2, highlighting roles in junction assembly, immune-cell migration, cell-cycle control and transporter activation (Sprowl et al., 2016; Kook et al., 2024; Zhao et al., 2020).

## Structure

YES1 displays the canonical SFK architecture:  
• N-terminal SH4 domain containing myristoylation/palmitoylation sites for membrane anchoring.  
• A short unique region.  
• SH3 domain (binds proline-rich motifs; contributes to autoinhibition).  
• SH2 domain (binds phosphotyrosine motifs).  
• C-terminal bilobed kinase (SH1) domain with conserved C-helix, activation loop and hydrophobic spine.  
Crystal structures of related SFKs and modelling support a dynamic, modular organisation (Bludau et al., 2022; Kukenshoner et al., 2017; Zhao et al., 2020).

## Regulation

• Activation-loop autophosphorylation promotes an open, active conformation.  
• CSK-mediated phosphorylation of a conserved C-terminal tyrosine induces intramolecular SH2 binding and autoinhibition.  
• Ubiquitination modulates stability and localisation.  
• Myristoylation/palmitoylation direct YES1 to membrane microdomains where receptor tyrosine kinases (EGFR, PDGFR, CSF1R, FGFR) activate it and position it near substrates (Kook et al., 2024; Bhullar et al., 2018).

## Function

Broadly expressed across tissues, YES1 is recruited downstream of multiple receptor tyrosine kinases. Key roles include:  
• Tight-junction assembly via PARD3 phosphorylation.  
• Support of adherens junctions through indirect CTNND1 phosphorylation.  
• Chemokine-induced T-cell migration by DPYSL2 phosphorylation.  
• Cell-cycle progression through CDK4 phosphorylation and contributions to G2/M and cytokinesis.  
• Enhancement of OCT2 transporter activity.  
Collectively, YES1 regulates growth, survival, adhesion, migration and division (Bludau et al., 2022; Kook et al., 2024; Sprowl et al., 2016; Wu et al., 2023).

## Inhibitors

Broad-spectrum Src inhibitors such as dasatinib inhibit YES1 but lack selectivity. Structure-guided screens are in progress to identify more specific YES1 inhibitors for overcoming tumour drug resistance (Chiba et al., 2015; Kukenshoner et al., 2017; Bhullar et al., 2018).

## Other Comments

YES1 is frequently amplified or overexpressed in cancers (e.g., lung, breast, colorectal, gastric), correlating with proliferation, metastasis and therapy resistance. Its status as a prognostic marker and therapeutic target has driven efforts to develop potent, selective inhibitors with minimal off-target effects (Kook et al., 2024; Bhullar et al., 2018; Chiba et al., 2015).

## References

Bhullar, K. S., Lagarón-Noa, E., McGowan, E. M., & Rupasinghe, H. P. (2018). Kinase-targeted cancer therapies (pp. 11-13).

Bludau, I., Liu, X., & Aebersold, R. (2022). The structural context of YES1 (pp. 21-23).

Bradley, M. (2019). Evolution of protein (pp. 1-2, 25).

Cann, M. J. (2017). Measuring kinase activity — a (pp. 37-44).

Chiba, Y., Ikarashi, Y., & Fukuoka, M. (2015). Identification of potential YES1 inhibitors (pp. 11-12).

Garmendia, I., Sahoo, S., & Ciomei, M. (2022). YES1: a novel oncogenic driver (pp. 1-4, 6-8).

Kook, I., Jang, H., & Lee, H. (2024). Emerging roles of YES1 (pp. 1-14).

Kukenshoner, T., Heim, J., & Wu, Y. (2017). Selective targeting of YES1 (pp. 30-35).

Sprowl, J. A., Jang, J. H., & Sparreboom, A. (2016). A phosphotyrosine switch (p. 10).

Wu, X., Guo, Y., & Yang, J. (2023). YES1-mediated CUL9 phosphorylation (pp. 13-14).

Zhao, J., Zhang, L., & Fang, W. (2020). Scribble subcellular localization (pp. 18-23, 98-100).