## Phylogeny

Dual-specificity tyrosine-regulated kinase 1A (DYRK1A) is a class I DYRK member within the CMGC protein-kinase branch. It is most closely related to DYRK1B and shows broader similarity to class II DYRK2-4 and HIPKs (Soundararajan et al., 2013; Aranda et al., 2011). Orthologues include Saccharomyces cerevisiae Yak1, Drosophila melanogaster minibrain (mnb) and Mus musculus Dyrk1a (Widowati et al., 2018; Lee et al., 2020).

## Reaction Catalyzed

1. ATP + protein-L-serine/threonine ⇌ ADP + protein-L-O-phosphoserine/threonine (Soundararajan et al., 2013).
2. ATP + protein-L-tyrosine ⇌ ADP + protein-L-O-phosphotyrosine (Deboever et al., 2022).

## Cofactor Requirements

Catalysis requires divalent cations; Mn²⁺ supports higher activity than Mg²⁺ in vitro (Aranda et al., 2011; Lee et al., 2020).

## Substrate Specificity

DYRK1A prefers the motif R-x(2)-S/T-P, with strong selection for Arg at ‑3/-2 and Pro at +1 (Ananthapadmanabhan et al., 2023; Widowati et al., 2018). Non-canonical sites are tolerated when Ala or Val occupies +1 (Ananthapadmanabhan et al., 2023). An obligatory cis autophosphorylation on Tyr321 within the YxY activation-loop motif is required for catalytic maturation (Aranda et al., 2011).

## Structure

The protein comprises an N-terminal DYRK-homology (DH) box essential for folding and autophosphorylation, a bilobal kinase domain, and a C-terminal region enriched in His, PEST and nuclear-localisation sequences (Ananthapadmanabhan et al., 2023; Aranda et al., 2011). Crystal structures of the catalytic domain (PDB 2WO6, 4YU2) display an active DFG-in conformation with phosphorylated Tyr321, an aligned hydrophobic spine and a correctly positioned αC-helix (Soundararajan et al., 2013; Evers et al., 2017). The His-rich low-complexity tract targets DYRK1A to nuclear speckles (Ananthapadmanabhan et al., 2023).

## Regulation

• Autophosphorylation on Tyr321 is essential for activation (Aranda et al., 2011).  
• Additional phosphorylation at Ser97 and Ser520 modulates activity/stability (Widowati et al., 2018).  
• SCF-FBXW7-mediated ubiquitination triggers proteasomal degradation (Aranda et al., 2011).  
• Calpain-1 C-terminal cleavage yields a hyperactive fragment (Lindberg & Meijer, 2021).  
• Interaction with the WD40 adaptor WDR68/DCAF7 affects localisation, while SRC-family kinases function upstream (Lindberg & Meijer, 2021; Lee et al., 2020).

## Function

DYRK1A is highly expressed in cerebral cortex, hippocampus and pancreatic islets, localising to both nucleus and cytoplasm with enrichment in nuclear speckles (Deboever et al., 2022; Ananthapadmanabhan et al., 2023). Reported substrates and pathways include:  
– DNA-damage response: phosphorylation of RNF169 limits TP53BP1 accrual and favours homologous-recombination repair (Ananthapadmanabhan et al., 2023).  
– Transcription: acts as a C-terminal-domain kinase for RNA-polymerase II (Deboever et al., 2022).  
– mRNA splicing: phosphorylates SRSF6, influencing alternative splicing such as tau exon 10 (Lindberg & Meijer, 2021).  
– Cell cycle and neurogenesis: phosphorylation of p27^Kip1 and cyclin D1 promotes neuronal differentiation and G₀ exit (Ananthapadmanabhan et al., 2023).

## Inhibitors

Harmine (nanomolar), INDY (low-micromolar indirubin derivative) and Leucettine-41 (sub-micromolar, brain-penetrant) are commonly used ATP-competitive inhibitors (Aranda et al., 2011; Deboever et al., 2022; Nguyen et al., 2017).

## Other Comments

The DYRK1A gene maps to chromosome 21; gene dosage increase contributes to cognitive deficits in Down syndrome, whereas haploinsufficiency causes an autosomal-dominant intellectual-disability syndrome with microcephaly (Lindberg & Meijer, 2021; Widowati et al., 2018). Pathogenic missense variants (H319Y, R467Q) abolish kinase activity, and truncations confer loss-of-function phenotypes (Lee et al., 2020). Hyperactive DYRK1A enhances tau and APP phosphorylation linked to Alzheimer’s disease and has context-dependent roles in cancer and β-cell regeneration (Deboever et al., 2022; Lindberg & Meijer, 2021).

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