## Phylogeny

Human DYRK3 (UniProt O43781) is classified within the CMGC kinase group, DYRK subfamily, class II branch that also contains DYRK2 and DYRK4 (kim2018crystalstructureof pages 1-6). Phylogenetic analyses place DYRK kinases closest to CLK and PRP4 subfamilies inside CMGC (becker1999structuralandfunctional pages 7-11). Orthologs are detected across eukaryotes, including Saccharomyces cerevisiae Yak1p, Drosophila melanogaster minibrain/dDyrk3, Caenorhabditis elegans MBK-2, Trypanosoma brucei class-2 DYRK, Danio rerio dyrk3, Mus musculus Dyrk3 and Homo sapiens DYRK3, indicating conservation before the last eukaryotic common ancestor (aranda2011dyrkfamilyof pages 2-3, han2012deepevolutionaryconservation pages 2-3). Manning et al. 2002 placed DYRK3 in the CMGC→DYRK clade of the human kinome (han2012deepevolutionaryconservation pages 9-9).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr ⇌ ADP + protein-O-phospho-Ser/Thr (substrate phosphorylation) (becker1998sequencecharacteristicssubcellular pages 1-1).  
ATP + DYRK3-L-Tyr ⇌ ADP + DYRK3-O-phospho-Tyr (intramolecular activation-loop autophosphorylation) (kim2018crystalstructureof pages 1-6).

## Cofactor Requirements

Catalysis requires Mg²⁺ for ATP coordination; no additional divalent cation dependence has been reported (kim2018crystalstructureof pages 9-13).

## Substrate Specificity

A kinome-wide consensus motif for DYRK3 has not been reported; the kinase phosphorylates serine/threonine residues within flexible, proline-rich segments of substrates. Experimentally validated sites include PRAS40 Thr246 in vitro and histone H2B Ser/Thr residues, while activation-loop Tyr321 undergoes autophosphorylation (kim2018crystalstructureof pages 18-22, becker1998sequencecharacteristicssubcellular pages 1-1).

## Structure

Crystal structures of human DYRK3 (PDB 5Y86 and 6EJ8) resolve residues 138-533 at 1.9 Å, revealing a bilobal kinase fold (kim2018crystalstructureof pages 22-31).  
– N-terminal auto-phosphorylation accessory (NAPA) domain: residues 154-172; promotes efficient Tyr321 autophosphorylation and shields a hydrophobic N-lobe surface (kim2018crystalstructureof pages 6-9).  
– DYRK homology (DH) box: residues 187-197; contributes to structural integrity typical of DYRK family kinases (kim2018crystalstructureof pages 6-9).  
– Catalytic domain: canonical CMGC motifs Lys178-Glu194 (β3-αC), HRD 291-293, DFG 309-311 and the activation-segment THEYxY sequence containing Tyr321 (kim2018crystalstructureof pages 22-31, becker1999structuralandfunctional pages 7-11).  
– Regulatory Ser350 within the C-lobe is surface-exposed; its phosphorylation increases thermal stability (kim2018crystalstructureof pages 18-22).  
– A MAPK-like insert between β7-β8 and a continuous hydrophobic spine are present, consistent with an active C-helix-in conformation (kim2018crystalstructureof pages 22-31).

## Regulation

Autophosphorylation  
– Tyr321: co-translational, essential for catalytic competence (kim2018crystalstructureof pages 1-6).  
– Ser350: increases protein stability and catalytic activity (kim2018crystalstructureof pages 18-22).

Other post-translational modifications  
– Reported ubiquitination events modulate stability, although specific lysines and E3 ligases remain undefined (unknownauthors2022regulationofposttranslational pages 174-174).

Localization and context-dependent control  
– Predominantly cytoplasmic; accumulates in stress granules under oxidative or arsenite stress and re-activates upon stress relief (kim2018crystalstructureof pages 1-6).

## Function

Expression is enriched in erythroid progenitors, testis, kidney and liver (zhang2005dyrkgenestructure pages 1-2). DYRK3 limits stress erythropoiesis: knockout mice display expanded CFU-E compartments and elevated reticulocyte output, whereas transgenic overexpression suppresses pro-erythroblast development (bogacheva2008dyrk3dualspecificitykinase pages 9-10). The kinase phosphorylates PRAS40 and histone H2B, linking it to mTORC1 pathway modulation and chromatin regulation (kim2018crystalstructureof pages 18-22, becker1998sequencecharacteristicssubcellular pages 1-1). DYRK3 translocates to stress granules and participates in dynamic control of membraneless organelles during cellular stress (kim2018crystalstructureof pages 1-6).

## Inhibitors

– Harmine: ATP-competitive inhibitor co-crystallised with DYRK3 (PDB 5Y86); binds deep hydrophobic ATP pocket (kim2018crystalstructureof pages 1-6).  
– Benzothiazole derivative “compound 53”: >90 % inhibition of DYRK3 at 10 µM; sub-micromolar potency against related DYRKs (demuro2021gsk3βfynand pages 21-23).  
– Leucettine analogues bind the ATP site; structural and selectivity data available from DYRK family complexes (tahtouh2012selectivitycocrystalstructures pages 15-16).

## Other Comments

The human DYRK3 gene contains four exons, representing one of the simplest architectures within the DYRK family (zhang2005dyrkgenestructure pages 1-2). DYRK3 dysregulation contributes to anaemia phenotypes, supporting its potential as a therapeutic target in haematological disorders (bogacheva2008dyrk3dualspecificitykinase pages 9-10).

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