## Phylogeny

DYRK1B belongs to the CMGC group of the eukaryotic kinome, which also includes cyclin-dependent kinases (CDKs), mitogen-activated protein kinases (MAPKs), and glycogen synthase kinase-3 (GSK3) (aranda2011dyrkfamilyof pages 1-2, grygier2025structuralperspectiveon pages 1-3). According to the classification by Manning et al. (2002), it is a member of the DYRK (dual-specificity tyrosine-regulated kinase) family (aranda2011dyrkfamilyof pages 1-2, yoshida2008rolefordyrk pages 5-6). The DYRK family is composed of three subfamilies: DYRKs, homeodomain-interacting protein kinases (HIPKs), and pre-mRNA processing protein 4 kinases (PRP4s) (aranda2011dyrkfamilyof pages 1-2). Within the DYRK subfamily, phylogenetic analyses place DYRK1B in the DYRK1 group (aranda2011dyrkfamilyof pages 1-2). It is considered a Class I DYRK, alongside its closest paralog, DYRK1A, with which it shares 85% sequence identity (boni2020thedyrkfamily pages 7-9, kokkorakis2024mirkdyrk1bkinaseinhibitors pages 11-12).

## Reaction Catalyzed

DYRK1B is a kinase that catalyzes the transfer of the γ-phosphate group from ATP to the hydroxyl group of a specific serine or threonine residue on a substrate protein (grygier2025structuralperspectiveon pages 22-24, kokkorakis2024mirkdyrk1bkinaseinhibitors pages 15-17). The chemical reaction is: ATP + [protein]-L-serine/threonine = ADP + [protein]-O-phospho-L-serine/threonine (kokkorakis2024mirkdyrk1bkinaseinhibitors pages 15-17, grygier2025structuralperspectiveon pages 1-3).

## Cofactor Requirements

The catalytic activity of DYRK1B is dependent on ATP as the phosphate donor and requires a divalent metal ion cofactor (grygier2025structuralperspectiveon pages 1-3). The kinase can utilize either Mg²⁺ or Mn²⁺ for catalysis (kokkorakis2024mirkdyrk1bkinaseinhibitors pages 15-17, grygier2025structuralperspectiveon pages 9-12). These ions are coordinated by conserved residues, including Asp 307 and Asn 292, to facilitate ATP binding and hydrolysis (kokkorakis2024mirkdyrk1bkinaseinhibitors pages 15-17).

## Substrate Specificity

Based on comprehensive profiling of the human serine/threonine kinome, the substrate specificity motif for DYRK1B features a preference for a proline residue at the P+1 position relative to the phosphorylated serine or threonine (johnson2023anatlasof pages 3-4). The consensus motif also shows a preference for basic residues, such as arginine or lysine, at the P-3 position (johnson2023anatlasof pages 3-4). The atlas of substrate specificities provides the exact experimental motif for DYRK1B, which is characterized by both positive and negative selectivity for specific amino acids surrounding the phosphorylation site (johnson2023anatlasof pages 1-2).

## Structure

The crystal structure of the DYRK1B kinase domain (PDB ID: 8C2Z) exhibits a bilobal fold typical of CMGC kinases, consisting of a smaller N-terminal lobe and a larger C-terminal lobe with the active site located in the cleft between them (grygier2025structuralperspectiveon pages 6-9). The N-lobe is mainly composed of β-sheets and contains the catalytic lysine (Lys140), while the C-lobe is primarily α-helical (grygier2025structuralperspectiveon pages 6-9, kokkorakis2024mirkdyrk1bkinaseinhibitors pages 11-12). The full-length protein contains an N-terminal DYRK homology (DH) box, which is essential for autophosphorylation during kinase maturation, and a C-terminal PEST sequence that promotes rapid protein degradation (grygier2025structuralperspectiveon pages 1-3). Key features of the kinase domain include an active ‘DFG-in’ conformation, a gatekeeper phenylalanine residue (Phe190) that controls access to the ATP-binding pocket, and an activation loop containing a Y271-x-Y273 motif that undergoes autophosphorylation (grygier2025structuralperspectiveon pages 6-9, kokkorakis2024mirkdyrk1bkinaseinhibitors pages 11-12).

## Regulation

DYRK1B activity is primarily regulated by irreversible autophosphorylation of a tyrosine residue (Tyr273) in the activation loop’s YxY motif, an event that occurs during or immediately after translation (becker2018awake‐upcall pages 4-6, kokkorakis2024mirkdyrk1bkinaseinhibitors pages 1-2). This maturation step, supported by the N-terminal DH box, locks the kinase into a constitutively active conformation, after which it functions as a serine/threonine kinase on external substrates (kokkorakis2024mirkdyrk1bkinaseinhibitors pages 1-2). Kinase activity can be modestly enhanced by Rac1-MKK3 signaling and by ERK1/2-mediated phosphorylation at Ser421 (becker2018awake‐upcall pages 4-6). Activity is negatively regulated by the binding of Ran-binding protein M (RanBP9) (becker2018awake‐upcall pages 4-6). Regulation also occurs via two alternative promoters (pA and pB) and alternative splicing, which can produce kinase-inactive isoforms lacking parts of the kinase domain (aranda2011dyrkfamilyof pages 7-8). Subcellular localization further modulates function, with nuclear DYRK1B acting as a negative regulator of cell cycle progression and cytosolic DYRK1B acting as a prosurvival factor (aranda2011dyrkfamilyof pages 7-8).

## Function

DYRK1B is expressed ubiquitously, with high levels in skeletal muscle and testis (boni2020thedyrkfamily pages 1-3, kokkorakis2024mirkdyrk1bkinaseinhibitors pages 2-3). It negatively regulates cell cycle re-entry by phosphorylating and promoting the degradation of cyclin D1 at Thr288, while phosphorylating and stabilizing the CDK inhibitor p27Kip1 (becker2018awake‐upcall pages 4-6, vorwerk2024differentialregulationof pages 9-10). It also activates the DREAM complex by phosphorylating the LIN52 subunit at Ser28, which helps maintain quiescence (becker2018awake‐upcall pages 4-6). In myoblast differentiation, DYRK1B phosphorylates histone deacetylases HDAC5 and HDAC9, which derepresses the MEF2 transcription factor (aranda2011dyrkfamilyof pages 9-10). In cancer cells, it promotes survival by upregulating antioxidant genes such as SOD2 and SOD3, mediating the nuclear exclusion of FOXO tumor suppressors, and targeting tumor suppressors like NKX3.1 for degradation (becker2018awake‐upcall pages 4-6). Upstream regulators of DYRK1B expression include the MEK1 and RhoA signaling pathways (aranda2011dyrkfamilyof pages 7-8).

## Inhibitors

Known inhibitors of DYRK1B are primarily ATP-competitive and target the kinase’s ATP-binding pocket (aranda2011dyrkfamilyof pages 7-8). Harmine is a known inhibitor of DYRK family kinases (becker2018awake‐upcall pages 4-6). AZ191 is a potent inhibitor that has been co-crystallized with DYRK1B (PDB ID: 8C2Z) (kokkorakis2024mirkdyrk1bkinaseinhibitors pages 15-17). Other potent chemical scaffolds have been identified, including diaryl 1H-pyrazolo[3,4-b]pyridine derivatives (e.g., compound 8h, IC50 of 3 nM) and a 2,4-bisheterocyclic substituted thiophene (compound 48, IC50 of 70 nM), both of which show cytotoxic effects in cancer models (kokkorakis2024mirkdyrk1bkinaseinhibitors pages 11-12).

## Other Comments

DYRK1B is overexpressed in multiple solid tumors, including pancreatic, ovarian, colorectal, lung, breast, and prostate cancers (aranda2011dyrkfamilyof pages 9-10, boni2020thedyrkfamily pages 7-9). This overexpression, which is linked to tumor development and chemoresistance, is sometimes caused by genomic amplification of the DYRK1B locus at chromosome 19q13.2 (boni2020thedyrkfamily pages 7-9). In a non-cancer context, inactivating mutations in DYRK1B are a cause of abdominal obesity metabolic syndrome-3 (boni2020thedyrkfamily pages 7-9).

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