1. Phylogeny  
   DYRK1B, also known as Minibrain‐related kinase (Mirk), is a member of the dual‐specificity tyrosine phosphorylation‐regulated kinase (DYRK) family, which falls within the CMGC group of protein kinases. Its evolutionary lineage can be traced to a common eukaryotic ancestor, with orthologs present in invertebrates such as Drosophila and conserved in vertebrates including mammals. DYRK1B is classified as a Class I DYRK kinase and shares extensive sequence homology and domain organization with its closest paralog DYRK1A. Both kinases retain a conserved catalytic domain and regulatory motifs such as the DYRK homology (DH) box and nuclear localization signals, representing an evolutionarily maintained module for regulating cell cycle–associated and developmental processes (boni2020thedyrkfamily pages 1-3, boni2020thedyrkfamily pages 7-9).
2. Reaction Catalyzed  
   DYRK1B catalyzes the phosphorylation reaction in which the γ-phosphate group from ATP is transferred to specific amino acid residues on protein substrates. In addition to phosphorylating serine/threonine residues on substrates, DYRK1B also undergoes autophosphorylation on tyrosine residues that are essential for its full kinase activation. The overall chemical reaction can be summarized as: ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺ (boni2020thedyrkfamily pages 1-3, boni2020thedyrkfamily pages 17-18).
3. Cofactor Requirements  
   The kinase activity of DYRK1B is dependent on ATP as the phosphate donor and requires divalent metal ions as cofactors. In particular, Mg²⁺ is essential for the proper binding and positioning of ATP within the active site of the enzyme, enabling efficient catalysis (boni2020thedyrkfamily pages 1-3, hogg2023functionsofsrpkclkanddyrkkinasesin pages 2-4).
4. Substrate Specificity  
   DYRK1B displays dual-specificity kinase activity with a substrate specificity that is largely similar to that of its paralog DYRK1A. It preferentially phosphorylates serine/threonine residues within a consensus motif that is enriched in proline and basic residues. Studies indicate that the optimal substrate motif for Class I DYRK kinases is represented as RPx(S/T)PxP, requiring an arginine residue at the -3 position and a proline in the +1 position relative to the phosphoacceptor site. In addition to phosphorylating generic serine/threonine sites, DYRK1B has been shown to target regulatory proteins such as cyclin D1 by phosphorylating specific threonine residues, thereby influencing cell cycle progression (hogg2023functionsofsrpkclkanddyrkkinasesin pages 2-4, boni2020thedyrkfamily pages 18-20, boni2020thedyrkfamily pages 22-23).
5. Structure  
   The primary structure of DYRK1B is organized around a conserved catalytic kinase domain characteristic of the CMGC family. Preceding the kinase domain is a DYRK homology (DH) box motif that contributes to proper folding and catalytic competence. DYRK1B contains two nuclear localization signals (NLSs), which are critical for its dynamic subcellular distribution, and a C-terminal PEST-rich region that is thought to be involved in regulated proteolysis. Although high-resolution crystal structures specific to DYRK1B are not extensively reported, comparisons with DYRK1A suggest that the kinase domain adopts a bilobal architecture comprising an N-terminal lobe with predominantly β-strands and a C-terminal lobe with α-helices. The activation loop within the kinase domain undergoes autophosphorylation on a key tyrosine residue, an event that stabilizes the active conformation by aligning the hydrophobic spine and positioning the C-helix appropriately for catalysis. These structural features underpin the substrate recognition and catalytic mechanism of DYRK1B (boni2020thedyrkfamily pages 1-3, boni2020thedyrkfamily pages 25-26, hogg2023functionsofsrpkclkanddyrkkinasesin pages 6-7, oruganty2012designprinciplesunderpinning pages 6-7).
6. Regulation  
   DYRK1B is regulated primarily through an intramolecular autophosphorylation mechanism that targets tyrosine residues within the activation loop; such modification is required for the kinase to achieve full catalytic activity. In addition to autophosphorylation, DYRK1B activity is modulated by phosphorylation via upstream kinases, including ERK, which further enhances its catalytic performance. Post-translational modifications also serve to control its subcellular localization; DYRK1B shuttles between the cytoplasm and the nucleus in response to cellular cues such as DNA damage. This dynamic localization allows DYRK1B to associate with chromatin and regulate transcription under stress conditions. Furthermore, these regulatory mechanisms contribute to DYRK1B’s roles in control of the cell cycle and in mediating responses to chemotherapeutic stress (boni2020thedyrkfamily pages 17-18, boni2020thedyrkfamily pages 20-22, hogg2023functionsofsrpkclkanddyrkkinasesin pages 31-32).
7. Function  
   DYRK1B functions as a dual-specificity kinase with key roles in several critical cellular processes. It is essential for the repair of ribosomal DNA (rDNA) double-strand breaks and for maintaining rDNA copy number, thereby ensuring genomic stability. During the DNA damage response, DYRK1B contributes to transcriptional silencing by phosphorylating and promoting the accumulation of the histone methyltransferase EHMT2 at sites of double-strand breaks. In addition, DYRK1B enhances the transcriptional activities of factors such as TCF1/HNF1A and FOXO1. It also exerts inhibitory effects on epithelial cell migration and mediates the survival of colon carcinoma cells under conditions of limited mitogenic stimulation. Furthermore, DYRK1B acts as a negative regulator of the Sonic Hedgehog (SHH) and WNT1 pathways, a mode of action that facilitates adipogenesis. Finally, DYRK1B promotes the expression of gluconeogenic enzymes such as glucose-6-phosphatase catalytic subunit 1 (G6PC1), linking it to metabolic regulation (Information, boni2020thedyrkfamily pages 20-22, hogg2023functionsofsrpkclkanddyrkkinasesin pages 31-32).
8. Other Comments  
   Several small-molecule inhibitors targeting DYRK1B have been developed due to its implications in oncogenesis and metabolic disorders. Inhibitors such as AZ191 and benzothiazole-based compounds including INDY and BINDY have demonstrated ATP-competitive inhibition, providing valuable tools for dissecting DYRK1B function and offering potential routes for therapeutic intervention. Abnormal expression and activity of DYRK1B have been linked to poor prognoses in diverse cancers, including ovarian, pancreatic, and colon carcinomas, as well as to metabolic syndrome. These associations underscore the significance of DYRK1B as a therapeutic target, with ongoing research focused on improving inhibitor specificity and potency (boni2020thedyrkfamily pages 18-20, boni2020thedyrkfamily pages 25-26, nguyen2017dualspecificitytyrosinephosphorylationregulated pages 9-10, demuro2021gsk3βfynand pages 23-24).
9. References
10. boni2020thedyrkfamily pages 1-3
11. boni2020thedyrkfamily pages 7-9
12. boni2020thedyrkfamily pages 17-18
13. boni2020thedyrkfamily pages 18-20
14. boni2020thedyrkfamily pages 20-22
15. boni2020thedyrkfamily pages 25-26
16. hogg2023functionsofsrpkclkanddyrkkinasesin pages 2-4
17. hogg2023functionsofsrpkclkanddyrkkinasesin pages 6-7
18. hogg2023functionsofsrpkclkanddyrkkinasesin pages 31-32
19. nguyen2017dualspecificitytyrosinephosphorylationregulated pages 9-10
20. oruganty2012designprinciplesunderpinning pages 6-7
21. demuro2021gsk3βfynand pages 21-23
22. demuro2021gsk3βfynand pages 23-24

References

1. (boni2020thedyrkfamily pages 1-3): Jacopo Boni, Carlota Rubio-Perez, Nuria López-Bigas, Cristina Fillat, and Susana de la Luna. The dyrk family of kinases in cancer: molecular functions and therapeutic opportunities. Cancers, 12:2106, Jul 2020. URL: https://doi.org/10.3390/cancers12082106, doi:10.3390/cancers12082106. This article has 88 citations and is from a peer-reviewed journal.
2. (boni2020thedyrkfamily pages 17-18): Jacopo Boni, Carlota Rubio-Perez, Nuria López-Bigas, Cristina Fillat, and Susana de la Luna. The dyrk family of kinases in cancer: molecular functions and therapeutic opportunities. Cancers, 12:2106, Jul 2020. URL: https://doi.org/10.3390/cancers12082106, doi:10.3390/cancers12082106. This article has 88 citations and is from a peer-reviewed journal.
3. (boni2020thedyrkfamily pages 22-23): Jacopo Boni, Carlota Rubio-Perez, Nuria López-Bigas, Cristina Fillat, and Susana de la Luna. The dyrk family of kinases in cancer: molecular functions and therapeutic opportunities. Cancers, 12:2106, Jul 2020. URL: https://doi.org/10.3390/cancers12082106, doi:10.3390/cancers12082106. This article has 88 citations and is from a peer-reviewed journal.
4. (hogg2023functionsofsrpkclkanddyrkkinasesin pages 2-4): Elizabeth K. J. Hogg and Greg M. Findlay. Functions ofsrpk,clkanddyrkkinases in stem cells, development, and human developmental disorders. FEBS Letters, 597:2375-2415, Sep 2023. URL: https://doi.org/10.1002/1873-3468.14723, doi:10.1002/1873-3468.14723. This article has 7 citations and is from a peer-reviewed journal.
5. (boni2020thedyrkfamily pages 18-20): Jacopo Boni, Carlota Rubio-Perez, Nuria López-Bigas, Cristina Fillat, and Susana de la Luna. The dyrk family of kinases in cancer: molecular functions and therapeutic opportunities. Cancers, 12:2106, Jul 2020. URL: https://doi.org/10.3390/cancers12082106, doi:10.3390/cancers12082106. This article has 88 citations and is from a peer-reviewed journal.
6. (boni2020thedyrkfamily pages 20-22): Jacopo Boni, Carlota Rubio-Perez, Nuria López-Bigas, Cristina Fillat, and Susana de la Luna. The dyrk family of kinases in cancer: molecular functions and therapeutic opportunities. Cancers, 12:2106, Jul 2020. URL: https://doi.org/10.3390/cancers12082106, doi:10.3390/cancers12082106. This article has 88 citations and is from a peer-reviewed journal.
7. (boni2020thedyrkfamily pages 25-26): Jacopo Boni, Carlota Rubio-Perez, Nuria López-Bigas, Cristina Fillat, and Susana de la Luna. The dyrk family of kinases in cancer: molecular functions and therapeutic opportunities. Cancers, 12:2106, Jul 2020. URL: https://doi.org/10.3390/cancers12082106, doi:10.3390/cancers12082106. This article has 88 citations and is from a peer-reviewed journal.
8. (boni2020thedyrkfamily pages 7-9): Jacopo Boni, Carlota Rubio-Perez, Nuria López-Bigas, Cristina Fillat, and Susana de la Luna. The dyrk family of kinases in cancer: molecular functions and therapeutic opportunities. Cancers, 12:2106, Jul 2020. URL: https://doi.org/10.3390/cancers12082106, doi:10.3390/cancers12082106. This article has 88 citations and is from a peer-reviewed journal.
9. (demuro2021gsk3βfynand pages 21-23): Stefania Demuro, Rita M. C. Di Martino, Jose A. Ortega, and Andrea Cavalli. Gsk-3β, fyn, and dyrk1a: master regulators in neurodegenerative pathways. International Journal of Molecular Sciences, 22:9098, Aug 2021. URL: https://doi.org/10.3390/ijms22169098, doi:10.3390/ijms22169098. This article has 68 citations and is from a peer-reviewed journal.
10. (hogg2023functionsofsrpkclkanddyrkkinasesin pages 31-32): Elizabeth K. J. Hogg and Greg M. Findlay. Functions ofsrpk,clkanddyrkkinases in stem cells, development, and human developmental disorders. FEBS Letters, 597:2375-2415, Sep 2023. URL: https://doi.org/10.1002/1873-3468.14723, doi:10.1002/1873-3468.14723. This article has 7 citations and is from a peer-reviewed journal.
11. (hogg2023functionsofsrpkclkanddyrkkinasesin pages 6-7): Elizabeth K. J. Hogg and Greg M. Findlay. Functions ofsrpk,clkanddyrkkinases in stem cells, development, and human developmental disorders. FEBS Letters, 597:2375-2415, Sep 2023. URL: https://doi.org/10.1002/1873-3468.14723, doi:10.1002/1873-3468.14723. This article has 7 citations and is from a peer-reviewed journal.
12. (oruganty2012designprinciplesunderpinning pages 6-7): Krishnadev Oruganty and Natarajan Kannan. Design principles underpinning the regulatory diversity of protein kinases. Philosophical Transactions of the Royal Society B: Biological Sciences, 367:2529-2539, Sep 2012. URL: https://doi.org/10.1098/rstb.2012.0015, doi:10.1098/rstb.2012.0015. This article has 47 citations and is from a domain leading peer-reviewed journal.
13. (nguyen2017dualspecificitytyrosinephosphorylationregulated pages 9-10): Thu Lan Nguyen, Corinne Fruit, Yann Hérault, Laurent Meijer, and Thierry Besson. Dual-specificity tyrosine phosphorylation-regulated kinase 1a (dyrk1a) inhibitors: a survey of recent patent literature. Expert Opinion on Therapeutic Patents, 27:1183-1199, Aug 2017. URL: https://doi.org/10.1080/13543776.2017.1360285, doi:10.1080/13543776.2017.1360285. This article has 70 citations and is from a peer-reviewed journal.
14. (demuro2021gsk3βfynand pages 23-24): Stefania Demuro, Rita M. C. Di Martino, Jose A. Ortega, and Andrea Cavalli. Gsk-3β, fyn, and dyrk1a: master regulators in neurodegenerative pathways. International Journal of Molecular Sciences, 22:9098, Aug 2021. URL: https://doi.org/10.3390/ijms22169098, doi:10.3390/ijms22169098. This article has 68 citations and is from a peer-reviewed journal.