1. Phylogeny  
   DYRK1A is a highly conserved member of the dual‐specificity tyrosine phosphorylation‐regulated kinase (DYRK) family, which belongs to the CMGC group of serine/threonine kinases. Orthologs of DYRK1A have been identified across eukaryotic species ranging from yeast (e.g., Yak1p) through invertebrates such as Drosophila – where the ortholog is known as minibrain (mnb) – to vertebrates including rodents and humans, where the human protein exhibits approximately 99% sequence identity with its rodent counterpart (park2009functionandregulation pages 1-2, dierssen2006dyrk1a(dualspecificitytyrosinephosphorylated pages 1-3). Within the human kinome, DYRK1A is classified as one of the two members of class I DYRKs (the other being DYRK1B), in contrast to the class II DYRKs (DYRK2, DYRK3, and DYRK4); this subdivision reflects differences in domain composition and autophosphorylation mechanisms (lindberg2021dualspecificitytyrosinephosphorylationregulated pages 2-4, galceran2003themnbdyrk1aprotein pages 1-4). Its evolutionary conservation is apparent in the retention of a central catalytic domain, flanked by regulatory motifs such as the DYRK homology (DH) box that are conserved even in distantly related species, underscoring its fundamental role in cellular signaling pathways (dierssen2006dyrk1a(dualspecificitytyrosinephosphorylated pages 7-8, deboever2022theomnipresenceof pages 1-3).
2. Reaction Catalyzed  
   DYRK1A catalyzes phosphorylation reactions in which the terminal phosphate from ATP is transferred to a hydroxyl group of protein substrates. In this process, ATP and a hydroxyl-containing protein yield ADP and a phosphorylated protein, with the release of a proton. Although DYRK1A exhibits dual specificity in that it autophosphorylates on tyrosine residues in its activation loop and phosphorylates exogenous substrates predominantly on serine/threonine residues, the overall catalytic reaction can be summarized as follows: ATP + [protein]-OH → ADP + [protein]-O-phosphate + H⁺ (abbassi2015dyrk1ainneurodegeneration pages 7-10, ionescu2012dyrk1akinaseinhibitors pages 1-2).
3. Cofactor Requirements  
   The catalytic activity of DYRK1A is ATP-dependent and requires the presence of divalent metal ions, with Mg²⁺ acting as a critical cofactor. The binding of Mg²⁺ facilitates the proper orientation of ATP in the active site, thereby enabling the efficient transfer of the phosphate group to the target protein substrate (abbassi2015dyrk1ainneurodegeneration pages 7-10, ionescu2012dyrk1akinaseinhibitors pages 1-2).
4. Substrate Specificity  
   DYRK1A exhibits a strict substrate specificity characterized by its preference for phosphorylating serine or threonine residues when the target peptide contains specific adjacent amino acids. Notably, DYRK1A prefers a proline residue at the P+1 position relative to the phosphorylation site and a positively charged arginine at the P-3 position. This specificity is captured in a consensus motif, often described as RPX(S/T)P, where “X” can be variable, yet the presence of arginine in upstream positions and proline immediately downstream is critical for substrate recognition (abbassi2015dyrk1ainneurodegeneration pages 7-10, ananthapadmanabhan2023insightsfromthe pages 2-3). In addition to these sequence requirements, DYRK1A phosphorylates a number of physiologically significant substrates including components of the transcriptional apparatus (e.g., the C-terminal domain of RNA polymerase II), spliceosomal proteins such as SRSF6, and proteins involved in DNA damage repair such as RNF169, reflecting its broad role in many cellular pathways (abbassi2015dyrk1ainneurodegeneration pages 10-13, ananthapadmanabhan2023insightsfromthe pages 12-13).
5. Structure  
   DYRK1A possesses a modular architecture comprised of five main regions. At the N-terminus, a bipartite nuclear localization signal (NLS) directs the protein to the nucleus, where many of its substrates reside. Following the NLS, the protein contains a central catalytic domain that spans several conserved subdomains (commonly numbered I–XI) and includes the critical activation loop. Within this activation loop, autophosphorylation occurs on tyrosine 321; this modification is essential for attaining a fully active conformation and ensuring constitutive activity once synthesized (abbassi2015dyrk1ainneurodegeneration pages 7-10, dierssen2006dyrk1a(dualspecificitytyrosinephosphorylated pages 1-3). Downstream of the kinase domain, a proline-glutamic acid-serine-threonine-rich (PEST) domain is present, which is believed to signal for rapid proteolytic degradation. Moreover, DYRK1A features a unique consecutive histidine repeat region; this histidine-rich domain has been implicated in directing the kinase to nuclear speckles, which are subnuclear compartments enriched in pre-mRNA splicing factors. Finally, a serine/threonine-rich region is located at the C-terminus, whose function remains less well defined (abbassi2015dyrk1ainneurodegeneration pages 1-7, ananthapadmanabhan2023insightsfromthe pages 1-2). Structural studies, including crystallographic analyses that have captured the ATP-binding site and key hinge regions, have provided significant insight into the spatial organization of the catalytic domain and the unique features that distinguish DYRK1A from other kinases within the CMGC group (czarna2018novelscaffoldsfor pages 35-40, walte2013mechanismofdual pages 1-2).
6. Regulation  
   The regulation of DYRK1A is orchestrated primarily through autophosphorylation and post-translational modifications. A hallmark regulatory mechanism is the autophosphorylation of a key tyrosine residue (Tyr321) within the activation loop, an event that occurs co-translationally and is crucial for initiating full catalytic activity (abbassi2015dyrk1ainneurodegeneration pages 7-10, himpel2001identificationofthe pages 8-8). In addition, DYRK1A undergoes further autophosphorylation at a serine residue (Ser520), which enhances its kinase activity through the recruitment and binding of 14-3-3 proteins. This interaction stabilizes the active conformation and may protect the enzyme from dephosphorylation (abbassi2015dyrk1ainneurodegeneration pages 24-28, deboever2022theomnipresenceof pages 14-15). Transcriptional regulation also plays a role in modulating DYRK1A levels, as its gene dosage is critical; overexpression, as observed in Down syndrome resulting from trisomy 21, leads to elevated kinase activity, while haploinsufficiency is linked to neurodevelopmental defects (dierssen2006dyrk1a(dualspecificitytyrosinephosphorylated pages 7-8, ananthapadmanabhan2023insightsfromthe pages 12-13). In addition to intrinsic modifications, DYRK1A expression and activity are influenced by interactions with various regulatory proteins and transcription factors, including positive regulators such as E2F1 and negative regulators such as AP4, which further modulate its cellular abundance and functional output (abbassi2015dyrk1ainneurodegeneration pages 7-10, deboever2022theomnipresenceof pages 16-18).
7. Function  
   DYRK1A is a multifunctional kinase that plays pivotal roles in several critical cellular pathways. In the context of the central nervous system, DYRK1A is abundantly expressed during embryonic development and in adult brain regions such as the neocortex, hippocampus, olfactory bulb, and cerebellum. Its activity is essential for the regulation of neuronal proliferation, differentiation, and synaptogenesis. One well-documented role is its regulation of double-strand break (DSB) repair: DYRK1A phosphorylates the E3 ubiquitin ligase RNF169, thereby enhancing its ability to block the accumulation of TP53BP1 at sites of DNA damage, which in turn promotes repair through homologous recombination (abbassi2015dyrk1ainneurodegeneration pages 17-21, ananthapadmanabhan2023insightsfromthe pages 10-12). In addition, DYRK1A acts as a C-terminal domain (CTD) kinase by phosphorylating the CTD of the largest subunit of RNA polymerase II (POLR2A), positively influencing transcriptional regulation and gene expression (abbassi2015dyrk1ainneurodegeneration pages 24-28, ananthapadmanabhan2023insightsfromthe pages 12-13). Furthermore, DYRK1A modulates alternative splicing events through the phosphorylation of splice factors such as SRSF6, thereby affecting the splicing patterns of key neuronal transcripts (abbassi2015dyrk1ainneurodegeneration pages 40-45, ananthapadmanabhan2023insightsfromthe pages 3-4). The kinase also phosphorylates substrates involved in cell cycle control, including factors that regulate the G1/S transition, contributing to the decision between proliferation and differentiation in neural progenitor cells (abbassi2015dyrk1ainneurodegeneration pages 10-13, dierssen2006dyrk1a(dualspecificitytyrosinephosphorylated pages 8-10). In addition to its well-characterized roles in neuronal development and DNA repair, DYRK1A has been implicated in the phosphorylation of tau protein and the amyloid precursor protein (APP), processes that are central to the pathogenesis of Alzheimer’s disease (stotani2016dyrk1ainhibitionas pages 1-2, smith2012recentadvancesin pages 1-2). Overall, DYRK1A functions in diverse cellular contexts including transcriptional regulation, mRNA splicing, and DNA damage response, with its enzymatic activity impacting both developmental and stress response pathways (abbassi2015dyrk1ainneurodegeneration pages 13-17, park2009functionandregulation pages 1-2).
8. Other Comments  
   Several selective inhibitors of DYRK1A have been developed with potential therapeutic applications in neurodegeneration, Down syndrome, and cancer. Notable examples include natural product derivatives such as harmine and epigallocatechin gallate (EGCG), as well as synthetic compounds like leucettine L41, INDY, and various pyrido-pyrimidine scaffolds (ionescu2012dyrk1akinaseinhibitors pages 1-2, czarna2018novelscaffoldsfor pages 1-4). These inhibitors often function through ATP-competitive binding within the kinase’s active site, although challenges remain regarding selectivity due to structural similarities among kinases within the CMGC group. Elevated DYRK1A expression resulting from trisomy 21 is well recognized as a contributing factor in Down syndrome-associated neurodevelopmental defects, and animal models overexpressing DYRK1A exhibit cognitive impairments and altered neuronal morphology (galceran2003themnbdyrk1aprotein pages 1-4, park2009functionandregulation pages 1-2). Conversely, mutations that result in reduced DYRK1A activity have been linked to conditions characterized by microcephaly and intellectual disability (ananthapadmanabhan2023insightsfromthe pages 12-13). In addition, DYRK1A has been implicated in tumorigenesis, where its modulation of key substrates involved in cell cycle regulation and apoptosis may influence cancer cell proliferation and survival (fernandezmartinez2015dyrk1athedoubleedged pages 7-8, deboever2022theomnipresenceof pages 16-18). Ongoing drug discovery efforts, including fragment-based lead generation approaches, continue to refine the selection of compounds that specifically target DYRK1A while minimizing off-target effects on related kinases such as DYRK1B and CLKs (walmsley2021fragmentderivedselectiveinhibitors pages 1-2, tahtouh2021structure–activityrelationshipin pages 18-19).
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