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The chromosome 21 kinase DYRK1A: emerging roles in cancer biology and potential as a therapeutic target

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Abstract

Dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) is a serine/threonine kinase that belongs to the DYRK family of proteins, a subgroup of the evolutionarily conserved CMGC protein kinase superfamily. Due to its localization on chromosome 21, the biological significance of DYRK1A was initially characterized in the pathogenesis of Down syndrome (DS) and related neurodegenerative diseases. However, increasing evidence has demonstrated a prominent role in cancer through its ability to regulate biologic processes including cell cycle progression, DNA damage repair, transcription, ubiquitination, tyrosine kinase activity, and cancer stem cell maintenance. DYRK1A has been identified as both an oncogene and tumor suppressor in different models, underscoring the importance of cellular context in its function. Here, we review mechanistic contributions of DYRK1A to cancer biology and its role as a potential therapeutic target.

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Keywords

DYRK1A; quiescence; cell cycle; cell proliferation; tumor progression

Introduction

Dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) is a highly conserved kinase encoded on chromosome 21 in the Down syndrome critical region (DSCR). The DSCR contains a set of genes on the long arm of chromosome 21 (21q22.13–22.2) (1) that are associated with the Down syndrome (DS) phenotype (2). The *Drosophila* homolog of *DYRK1A*, *minibrain* (*mnb*), was identified as a contributor to postembryonic neurogenesis (3). In this report, the authors identified *mnb* as a novel serine/threonine protein kinase with significant homology to eukaryotic kinases that are known regulate cell growth and division; as such, they hypothesized that altered neuroblast proliferation observed in *mnb* kinase family mutants was due to a similar involvement in cell cycle regulation. Subsequent studies in mice demonstrated that complete loss of *Dyrk1a* is embryonically lethal, while *Dyrk1a* haploinsufficiency leads to intellectual disability, microcephaly, and growth defects, underscoring its critical role in neurologic development (4, 5). DYRK1A overexpression has also been implicated in neurodevelopmental delays, cognitive deficits, and motor impairment (6). These studies suggest that the impact of DYRK1A on various pathologies may occur in a dose-dependent fashion, whereby both under- and overexpression can drive disease. Cancer as a disease entity exemplifies this dynamic nature of DYRK1A and the heterogeneity of its function within different, and occasionally the same, cell types. In this review, we will discuss DYRK1A's structure, function, regulation, and role in cancer.

Domain Composition of DYRK1A

The DYRK family of kinases is evolutionarily conserved and divided into two categories: class I (DYRK1A and DYRK1B) and class II (DYRK2, DYRK3, and DYRK4) (7) (Figure 1). A key feature of DYRK family members is their ability to autophosphorylate tyrosine residues, rendering them catalytically active to phosphorylate other substrates on serine and threonine residues, hence the nomenclature of a dual-specificity kinase (8, 9). Class I DYRK proteins were historically defined by their putative nuclear localization signals (NLS), which precede the catalytic domain (10). They both contain a C-terminal PEST domain (11) and a WD-repeat domain, which binds the scaffolding protein DDB1 and CUL4 Associated Factor 7 (DCAF7) (12). This binding motif is critical for regulating nuclear localization of DYRK1A and maintaining protein levels (13). However, the presence of a NLS is in fact not unique to class I DYRKs, as both DYRK2 and DYRK4 have been shown to have NLS in subsequent loss-of-function studies (14, 15). Class II DYRKs also contain a NAPA domain that mediates autophosphorylation, although they lack the PEST domain (16).

DYRK1A is composed of three major domains (9). First, the DYRK homology (DH) box is essential for stabilizing tertiary structure in the N-terminus of autophosphorylated DYRK1A (9). Second, the conserved catalytic domain is required for kinase activity. Autophosphorylation of the critical activation-loop residue tyrosine 321 (Tyr321) within

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this domain takes place during or shortly after translation (8, 9, 17). Mutations in Tyr321 dramatically reduce the catalytic activity and impacts the overall function of its orthologs (9, 18). Third, DYRK1A has a PEST domain that facilitates DYRK1A degradation (10). In addition, DYRK1A contains a N-terminus NLS and a second within the catalytic domain (10), a C-terminal histidine repeat that promotes protein localization into nuclear speckles (19), and a Ser/Thr rich sequence that seems to regulate catalytic activity (20).

Regulation of DYRK1A

Transcriptional Regulation—Several proteins have been identified as upstream regulators of *DYRK1A* expression. RE1-silencing transcription factor (REST), also known as neuron-restrictive silencer factor (NRSF), is a zinc finger protein that acts as a master repressor of neuronal genes in differentiated non-neuronal tissues (21). REST activates *DYRK1A* transcription by binding to a neuron-restrictive silencer element located in the *DYRK1A* promoter region (22). In a negative feedback loop, DYRK1A can then phosphorylate REST, leading to its degradation (22). Using a transgenic mouse model of *Dyrk1a* overexpression, DYRK1A was found to interact with the SWI/SNF complex, which can bind REST, affecting its expression and dysregulating neuronal gene expression (23). However, this may not entirely be mediated by DYRK1A kinase activity. Separately, in embryonic stem cells and mice that model partial trisomy 21, REST was reported to be downregulated in a DYRK1A dose-dependent fashion (24). Consequently, the increase in DYRK1A expression and downregulation of REST was associated with a reduction in expression of pluripotency regulators and enhanced endoderm and mesoderm differentiation.

Myocyte-specific enhance factor 2D (MEF2D) is a transcription factor initially determined to be essential for muscle differentiation in both embryogenesis and adult regeneration (25) but was also found to promote post-mitotic neuronal survival (26). Of note, MEF2D upregulates *DYRK1A* expression in glioblastoma cells through a MEF2D responsive element in the promoter region of DYRK1A (27). The same group demonstrated that DYRK1A phosphorylates MEF2D at Ser251 and that increased DYRK1A expression or activity is inversely correlated with MEF2D transcriptional in HEK293 and U87MG cells, which was phenocopied by expression of phosphomimetic and phosphodeficient Ser 251 alleles (28). This phosphorylation event results in dissociation of MEF2D from DNA and decreased transactivation, demonstrating another negative feedback mechanism of a transcriptional activator.

Additionally, a recent kinase-focused CRISPR screen in *KMT2A*-rearranged B-cell acute lymphoblastic leukemia (B-ALL) cells identified a dependency on DYRK1A (29). ChIP-Seq revealed that the *KMT2A-AFF1* fusion complex directly binds the DYRK1A promoter and regulates its transcription. Notably, DYRK1A expression levels were lower in *KMT2A*-rearranged B-ALLs than in other B-ALL subtypes. The authors also demonstrated that chemical inhibition of DYRK1A suppressed the growth of B-ALL cells with this rearrangement.

While the exact interplay between DYRK1A and its upstream transcriptional regulators requires investigation in the context of cancer. Several of these regulators are involved in tissue specific differentiation and drive a negative feedback mechanism after activation of

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DYRK1A expression. These regulators also demonstrate conflicting oncogenic and tumor suppressor roles in a cell-dependent context; for example, REST promotes central nervous system tumors yet is reported to have anti-tumor properties in lung, breast, and colon cancer (21).

Regulation via Ubiquitin—Beyond transcriptional regulation, DYRK1A levels are also tightly controlled at the protein level through ubiquitination. $SCF^{\beta TrCP}$, an E3 ubiquitin ligase that promotes neuronal development by targeting REST for degradation in embryonic and neural stem cells (30), has also been shown to ubiquitinate and promote degradation of DYRK1A in HEK293 cells (31). As expected, DYRK1A protein levels negatively correlate with $SCF^{\beta TrCP}$ throughout the cell cycle, contributing to increased DYRK1A levels in G_0/G_1 and decreased levels in S and G_2/M. Similar to DYRK1A, $SCF^{\beta TrCP}$ has also been found to act in an oncogenic or tumor suppressor role in different cancers depending on its substrates (32), perhaps reflecting an antagonistic relationship between the two proteins, although this remains to be examined.

Another E3 ubiquitin ligase, TRAF2, which has been implicated in inflammation-mediated tumor growth (33), facilitates K63-linked ubiquitination of DYRK1A, promoting its translocation to a number of subcellular structures including membranous vesicles such as endosomes (34). Once localized to an endosome, DYRK1A can phosphorylate Sprouty2 at the Thr75 residue thereby negatively regulating endocytosis and recycling of EGFR thereby leading to its stabilization; this in turn promotes growth of glioma cell lines. Moreover, TRAF2 knockdown phenocopies EGFR degradation seen with DYRK1A knockdown in these cell lines. As such, loss of DYRK1A signaling by genetic and pharmacologic approaches slowed growth of glioma cell lines, which could not be rescued by TRAF2 overexpression.

A recent study reported that p53 activation leads to degradation of DYRK1A and subsequent downregulation of EGFR-ERK signaling, leading to cellular senescence in vitro and in vivo (35). It was also shown that MDM2, a p53 transcriptional target and ubiquitin ligase, directly binds DYRK1A and promotes its polyubiquitination. MDM2 can also bind p53 in a negative feedback loop; however, the use of Nutlin-3a, which selectively disrupts MDM2-p53 binding but not MDM2-DYRK1A binding, led to p53 activation and increased *MDM2* expression, ultimately causing DYRK1A degradation. Moreover, a single study in embryonic neuronal cells proposed that DYRK1A phosphorylates p53 at Ser15 (36) to cause cell cycle arrest. While this does invoke the possibility of DYRK1A as a regulator of p53 signaling, further studies are needed to more precisely define the relationship between DYRK1A and p53 in different cellular contexts.

Contributions of DYRK1A to normal and malignant cell growth

DYRK1A is associated with a multitude of tumors (Table 1), where it acts by modifying proteins that play key roles in cellular processes such as cell cycle, DNA damage repair, pre-mRNA splicing, transcription, angiogenesis, and protein stability (Figure 2).

DYRK1A contributes to cell cycle regulation—The DREAM (dimerization partner, RB-like, E2F and multi-vulval class B) complex is a group of proteins that assemble in G_0

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to repress cell cycle dependent gene expression and cell cycle progression (37). In addition, a critical component of the multi-vulval class B (MuvB) subunit of the DREAM complex is LIN52, which was shown to be phosphorylated by DYRK1A at Ser28 (38). Inhibition of DYRK1A or expression of a phosphodeficient allele of LIN52 (Ser28Ala) disrupted the assembly of the DREAM complex and significantly reduced the ability of cells to enter quiescence. Moreover, overexpression of a kinase-inactive allele of DYRK1A (Lys188Arg) led to increased proliferation of U2OS cells, while overexpression of a wild-type allele reduced proliferative capacity by half. This interplay between DYRK1A and the DREAM complex may not be limited to quiescence; co-expression of oncogenic HRAS with either DYRK1A Lys188Arg or LIN52 Ser28Ala, both of which have dominant-negative activity, was also associated with reduced cellular senescence. Furthermore, DYRK1A-mediated DREAM complex assembly contributes to ovarian cancer dormancy as DYRK1A inhibition reduced spheroid viability and restored sensitivity to chemotherapy targeting actively proliferating cells, suggestive of cells exiting quiescence (39).

Cyclins are another set of critical DYRK1A substrates. For example, DYRK1A has been shown to prolong G_1 by phosphorylating and degrading cyclin D1 (40), and sustained phosphorylation of cyclin D1 and $p27^{Kip1}$ by DYRK1A in neuroblastoma and neural stem cells decreased proliferation and increased differentiation (41).

DYRK1A also orchestrates early lymphopoiesis through phosphorylation of cyclin D3 (42). Highly proliferative lymphoid precursor cells known as large pre-B cells and double-negative (DN) thymocytes normally enter quiescence to facilitate maturation into small pre-B cells and double-positive (DP) thymocytes, respectively. In the absence of DYRK1A, B and T cell maturation are halted at the large pre-B cell and DN thymocyte stages, diminishing the production of small pre-B cells, DP thymocytes, and more differentiated lymphocytes. In this context, DYRK1A promotes quiescence through phosphorylation of cyclin D3, at Thr283, which resides in a phosphodegron motif conserved across all D-type cyclins, thereby leading to its ubiquitination and proteasomal-mediated degradation. Consequently, loss or inhibition of DYRK1A impaired quiescence and maturation of large pre-B cells and DN thymocytes through de-repression of E2F-mediated gene transcription in a cell cycle-dependent manner (42). Though this mechanism was paralleled in both B and T cell lineages, curiously it was not seen in myeloid cells. Although DYRK1A-deficient lymphocyte precursors had impaired ability to enter quiescence, they had reduced proliferation compared to control cells and accumulated in G_2/M, suggesting a concomitant late cell cycle defect.

DYRK1A has also been reported to phosphorylate the ubiquitin ligase CDC23, which mediates mitotic protein degradation, at Ser588 in the glioblastoma cell line U251 (43). In this model, DYRK1A inhibition decreased Ser588 phosphorylation, impairing APC complex assembly, thus preventing degradation of cyclin B and subsequently causing hyperactivation of CDK1. Indeed, DYRK1A inhibition promoted tumor growth and the fraction of Ki67-positive cells in this study.

Taken together, DYRK1A has diverse, non-redundant roles in the cell cycle by regulating the balance between cell cycle entry and quiescence, with substrates including LIN52, cyclin

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D1, cyclin D3, and CDC23. However, the ability of DYRK1A to promote or inhibit tumor growth and survival in these roles depends on the cellular context. Nevertheless, given the fundamental importance of cell cycle regulation in cancer biology, DYRK1A remains a promising target.

DYRK1A contributes to the DNA damage response—Recent studies have shed light on the role of DYRK1A in DNA damage response and apoptosis. Activated Forkhead box proteins (FOXO) proteins affect the cell cycle and proliferation in colon cancer, glioblastoma, osteosarcoma, acute myeloid leukemia, and head and neck squamous cell carcinoma (HNSCC) (44). As a transcription factor, FOXO1 plays a critical role in activating genes related to cell proliferation and apoptosis. During the G_2/M phase, FOXO1 acts as a DNA damage sensor and slows cell cycle progression to accommodate DNA repair or trigger apoptosis (45). DYRK1A phosphorylates FOXO1 at Ser329 in humans (orthologous to Ser326 in mice) and promotes its nuclear export and degradation (46, 47). When DYRK1A activity is ablated in normal pre-B cells, this increases the expression of FOXO1 transcriptional targets such as *GADD45A, CCNG2*, and *BCL2L11* to cause a G_2/M halt in response to cell cycle dysregulation and DNA damage accumulation without substantially increasing apoptosis; however, loss of both FOXO1 and DYRK1A activity preferentially kills B-ALL cells through increased sensitivity to replicative stress (46). Moreover, DYRK1A inhibition was found to sensitize leukemic cells to conventional chemotherapies that induce genotoxic stress.

Quantitative mass spectrometry revealed interactions of DYRK1A with numerous proteins involved in DNA damage repair, including RNF169, an E3 ubiquitin ligase that is an essential component of the cellular response to DNA double-stranded breaks (DSB) (48–51). DYRK1A was found to be recruited to sites of DNA damage through this interaction with RNF169. Moreover, knockdown of DYRK1A conferred increased sensitivity to ionizing radiation in colony formation assays (48). DYRK1A has also been linked to the DNA damage response via its phosphorylation of Sirtuin 1 (SIRT1) at Thr522, resulting in deacetylation of p53 in U2OS cells (52). Thus, there is accumulating evidence for the role of DYRK1A in regulating DNA damage through several distinct substrates.

DYRK1A regulates transcription and cell signaling—DYRK1A has been reported to regulate transcription through kinase dependent and independent interactions with RNA polymerase II (RNAPII) (53). ChIP-Seq data in T98G and HeLa cells revealed that DYRK1A is recruited to the promoters of ribosomal biogenesis and translation regulation and that its biding sites are enriched for the palindromic TCTCGCGAGA sequence. This study also revealed that DYRK1A phosphorylates the carboxy-terminal domain (CTD) of RNAPII at Ser2 and Ser5. A reduction in phosphorylation of these two residues by DYRK1A knockdown was found to impair the ability of RNAPII to associate with promoters. More recently, Lu et al demonstrated that DYRK1A contains a histidine-rich domain (HRD), which allows it to form phase-separated liquid droplets in vitro and in cells, thereby promoting highly efficient hyperphosphorylation of the RNAPII CTD (54). Deletion of the HRD reduced both CTD phosphorylation and co-immunoprecipitation of RNAPII, though did not affect DCAF7 co-immunoprecipitation. However, another group

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reported that DCAF7 promotes DYRK1A-RNAPII interaction and is essential for myogenic differentiation and expression of key myogenic genes, including *MYH2*, *CAV3*, and *MYOG* (55), suggesting that there may be multiple mechanisms by which DYRK1A localizes to RNAPII in subcellular compartments.

DYRK1A also regulates transcription factors that control cell signaling. Nuclear factor of activated T-cells (NFAT) is phosphorylated by DYRK1A and subsequently exported from the nucleus, preventing transactivation (56–58). Impaired NFAT nuclear export leads to a more invasive phenotype of the breast cancer cell line 4T1 (59) through upregulation of the metalloproteinase ADAMTS1 (60). Increased levels of DYRK1A in DS also contributes to the development of acute megakaryoblastic leukemia (AMKL) through inhibition of NFAT signaling (61).

The transcription factor Signal Transducer and Activator of Transcription 3 (STAT3) is another DYRK1A substrate that regulates tumor proliferation. Constitutive activation of STAT3 has been reported in many cancers, including hematologic malignancies and solid tumors (62, 63), and correlates with a poor prognosis (64). Canonically, STAT3 is activated by JAK-mediated phosphorylation at Tyr705, resulting in its dimerization and translocation to the nucleus to activate transcription (65, 66). DYRK1A phosphorylates STAT3 at Ser727 (67, 68), a residue conserved in both humans and mice, and several studies show that phosphorylation of STAT3 at Ser727 is critical for STAT3 activity, including non-canonical mitochondrial pathways (69–71). Aberrant STAT3 activation due to hyperactivation of upstream tyrosine kinases, and overexpression of stimulatory receptor-ligand interactions promote tumor progression (72, 73). In a mouse model of DS, DYRK1A overexpression enhances STAT3 activity and promotes astrogliogenesis (74). In non-small cell lung cancer (NSCLC), DYRK1A inhibition decreases STAT3 activity and decreases NSCLC proliferation due to impaired EGFR/MET signaling (75). Recently, phosphorylation of STAT3 Ser727 by DYRK1A has been linked to survival of B-ALL tumor cells through maintenance of canonical Tyr705 signaling and by reducing cellular stress induced by reactive oxidative species (ROS) (46).

In a recent study, Li et. al examined the activity of B-cell activating factor (BAFF) in autoimmunity and B-ALL (76). They report that BAFF promotes non-canonical NF-kB signaling in a DYRK1A-dependent manner. Specifically, DYRK1A phosphorylates TRAF3, a protein involved in ubiquitin mediated degradation of a noncanonical NF-kB inducing kinase, at Ser29 and facilitates B-cell tumor development.

DYRK1A in angiogenesis—In 2009, Ryeom and colleagues proposed that DYRK1A and DSCR1, which contribute to calcium homeostasis, control angiogenesis, providing a potential explanation for the decreased incidence of solid tumors in people with DS (77). Another study found that inhibition or silencing of DYRK1A in primary endothelial cells led to decreased intracellular Ca^{2+} influx in response to VEGF and reduced downstream NFAT activation (78). Such modulation of $Ca^{2+/}$NFAT signaling by DYRK1A was discovered to be mediated through VEGF receptor 2 (VEGFR2) stability. Moreover, *Dyrk1a* haploinsufficient mice showed defects in developmental retinal vascularization, providing additional evidence that DYRK1A influences the angiogenic response (78). Finally, the kinase activity of

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DYRK1A is required for vascular formation in zebrafish via regulation of calcium signaling (79).

DYRK1A regulates tyrosine kinases involved in tumor growth—Major tyrosine kinase substrates of DYRK1A that drive tumor growth include c-MET and EGFR (75, 80). DYRK1A is upregulated in both pancreatic ductal adenocarcinoma (PDAC) and non-small cell lung cancer (NSCLC), where it has been associated with tumor growth and maintenance by modulating the activity of several downstream pathways. For example, DYRK1A expression is correlated with c-MET levels in the PANC-1 pancreatic cells, and DYRK1 knockdown led to reduced proliferation, suggesting that it may be a therapeutic target (80). In EGFR wild-type NSCLC cells, DYRK1A knockdown also decreased proliferation (75).

Like c-MET, EGFR degradation is also inhibited by DYRK1A(34). During adult neural progenitor cell division, DYRK1A inhibits EGFR degradation via phosphorylation of Thr75 on Sprouty2, a regulator of receptor tyrosine kinase turnover (81). In glioblastomas, increased DYRK1A expression correlated with increased EGFR levels, and inhibition of DYRK1A impaired self-renewal capacity in EGFR dependent glioblastoma cells (82). Conversely, in NSCLC, inhibition of DYRK1A reduced the levels of EGFR and MET, and consequently sensitized cells to AZD9291, an EGFR tyrosine kinase inhibitor (75). Of note, EGFR signaling is also required for Kras oncogene driven carcinogenesis in PDAC (83). Further studies have shown that EGFR cooperates and activates the AKT and STAT3 signaling pathways that together promote Kras driven oncogenic signals (83). As DYRK1A increases EGFR stability, these observations suggest an important tumor-inducing role of this pathway in PDAC as well.

DYRK1A regulates cancer stem cell-like properties—Recent data have shown that DYRK1A regulates the cancer stem cell population (84). Lee and colleagues discovered that DYRK1A-mediated phosphorylation of inhibitor of DNA binding 2 (ID2) at Thr27 blocks the ID2-VHL interaction and leads to HIF2α stabilization and cancer cell stemness in glioma (85). Downregulation of DYRK1A was found to increase HIF2α, suggesting that DYRK1A can act as a tumor suppressor in this setting. Similarly, DYRK1A induced cancer stem cell (CSC) differentiation by downregulating CDK5-SOX2 in the glioma line U251 (86). Conversely, DYRK1A inhibition in gliomas limited self-renewal capacity through decreased EGFR stability (82). DYRK1A may also induce stemness through REST (87), suggesting it can also function as an oncogene in gliomas. These data highlight DYRK1A's context and tumor-dependent action within cancers of the same origin. Beyond gliomas, DYRK1A can induce FGF2 to repress differentiation and promoted CSC self-renewal capacity in oropharyngeal squamous cell carcinoma (OSCC) Notably, DYRK1A inhibition abrogates CSC maintenance, increases sensitivity to chemotherapy, and suppresses migration of OSCC (88).

DYRK1A and splicing—DYRK1A localizes to nuclear speckles and phosphorylates several key splicing factors including SRSF1, SRSF2, SRSF6, and SF3B1 (19, 89–93). Several studies have shown that DYRK1A modulates alternative splicing in neurobiology; for example, DYRK1A promotes alternative splicing of Tau through modulation of SRSF1 and SRSF2 (90, 94). New data from Abdel-Wahab and colleagues demonstrate that

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venetoclax-resistant AML cell lines have enhanced sensitivity to DYRK1A and CDC2-like kinase (CLK) inhibition, possibly through SR proteins (95). Further effort into elucidating DYRK1A's impact in this process deserves special attention. (96).

Prospects for targeting DYRK1A

Given the multifaceted roles of DYRK1A in the phenotypes of DS, neurodegenerative diseases, and cancer, there has been significant interest in the development of potent and selective DYRK1A inhibitors (Table 2). In this section, we will review select DYRK1A-targeting therapies tested in cancer.

Natural compounds that inhibit DYRK1A—Several small molecules, including natural products, have been investigated for their ability to inhibit DYRK1A. For example, a clinical trial conducted in 2018 showed that epigallocatechine gallate (EGCG), a potent catechin found in green tea, improved visual recognition memory and working memory performance in patients with DS (97). While being a potent DYRK1A inhibitor *in vitro*, EGCG also binds and inhibits p38-regulated/activated protein kinase (PRAK)(98). EGCG has been tested both in vitro and in vivo in several cancers, including hepatocellular carcinoma, pancreatic cancer, prostate cancer, breast cancer, melanoma, head and neck cancer, and digestive cancers (99). In head and neck cancer, EGCG treatment was found to decrease cellular proliferation due to the suppression of the Notch pathway, while in triple negative breast cancer, EGCG induces apoptosis by scavenging ROS. However, EGCG has several disadvantages for *in-vivo* usage such as poor bioavailability and heterogeneous effects on signaling pathways.

Another widely used DYRK1A inhibitor for *in vitro* and *in vivo* studies has been a β-carboline alkaloid named harmine, an ATP-competitive inhibitor that was initially assayed for activity in Parkinson's disease (100). Harmine has been tested in multiple cancer subtypes, including breast, pancreatic, HNSCC and ovarian cancer and has been shown to effectively reduce tumor progression in mice (101). Although harmine is a potent DYRK1A inhibitor, it also targets other DYRKs and monoamine oxidase (MAO-A), resulting in side effects that limit its therapeutic potential (102). To overcome this limitation, several derivatives of harmine are being synthesized that are more selective for DYRK1A (103, 104).

The natural compound inhibitor L41, a type of leucettine, has potent activity against DYRK1A(105) as well as CLK. L41 has been found to decrease memory impairments and neurotoxicity in mice treated with $A\beta_{25-35}$ peptide that represents a non-transgenic model that mimics Alzheimer's disease (AD)-like toxicity (106). Indeed, L41 displays effective activity (IC_{50}=40nm) against U251 cells in vitro (43).

Race to develop selective inhibitors—Synthetic DYRK1A inhibitors Methyl 9-anilinothiazolo (5,4-*f*)quinazoline-2-carbimidates 1 and 2, commonly known as EHT 5372 and EHT 1610, have been shown to inhibit DYRK1A in neurologic disease (107) and in cancer. In PANC-1 tumor cells, EHT 5372 induced exit from quiescence and entry into the cell cycle while also increasing DNA damage and apoptosis (108). Exposure of murine pre-B cells to EHT 1610 recapitulated the phenotype seen upon *Dyrk1a* silencing, including

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loss of pre-B cell colony formation (42), and EHT 1610 also demonstrated anti-tumor activity in models of B-ALL (46). Moreover, treatment of *KMT2A*-rearranged B-ALL cell lines with EHT 1610 inhibited their proliferation similar to what was observed with genetic inhibition of DYRK1A using CRISPR (29). A more recent derivative of EHT 1610, FC162, displayed similar effects on B cell growth (105, 109).

CLK inhibitors target alternative splicing but demonstrate off-target effects on DYRK1A due to similarities in structure between their respective catalytic kinase domains (110, 111). CX-4945 (Silmitasertib), an orally bioavailable CLK inhibitor, exerts its effects through multiple survival pathways (112) and notably displays potent DYRK1A inhibition (IC_{50}=6.8nm). Thus far, CX-4945 has demonstrated efficacy across multiple tumor cell lines, including lymphoid, myeloid, and gastric tumor cells (113–117). Preliminary data from a phase Ib/II trial using CX-4945 with gemcitabine and cisplatin for patients with locally advanced or metastatic cholangiocarcinoma revealed improved outcomes (118). Furthermore, clinical trials in medulloblastoma (NCT03904862), multiple myeloma (NCT01199718, NCT00891280), and basal cell carcinoma (NCT03897036) are underway.

Finally, a number of other selective inhibitors have been reported though structure-based discovery (119–123). From these advanced studies, it appears that we are close to identifying clinically viable compounds for multiple indications, including metabolic, neurologic, and oncologic disorders.

It should be highlighted that most DYRK1A inhibitors also target DYRK1B, which is upregulated in many cancers and is considered to be tumorigenic (124). Similar to DYRK1A, DYRK1B regulates cell proliferation, cell cycle and has been shown to regulate ROS levels in response to stress (108). Due to the similar function and upregulation of these two DYRKs in cancer, it is unclear whether the effect mediated by these inhibitors is due to reduced activity of DYRK1A or DYRK1B. Development of more selective compounds and genetic studies to target each homolog individually are needed to clearly establish the activities of these two genes to cancer.

Summary

DYRK1A is linked to many cellular processes, including proliferation, self-renewal, DNA damage, transcriptional regulation, apoptosis, ubiquitination, cancer stem cell maintenance, and alternative splicing. However, DYRK1A can promote or inhibit tumor growth based on cancer subtype and stage. Since DYRK1A is a potent regulator of quiescence, DYRK1A inhibition in cancer has the potential to trigger relapse of dormant cancer cells. To exploit this possibility, one strategic therapeutic option might be to administer a DYRK1A inhibitor in parallel with chemotherapy. In this light, combination chemotherapy could enable targeting dormant cancer cells by pushing them out of quiescence and into cell cycling; this has recently been demonstrated in pre-clinical studies of B-ALL (46). Additionally, recent studies have shown that DYRK1A can enhance sensitivity to radiation, and thus DYRK1A inhibition may offer a novel approach to radiosensitization (48, 49). Future studies must address ongoing issues with DYRK1A as a potential therapeutic target in cancer, including distinguishing off-target/on-target effects of inhibitors in vivo, characterizing the effects

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of DYRK1A inhibition in normal tissues, elucidating redundant and non-redundant roles of DYRK1A and DYRK1B in malignancy, and optimizing the pharmacokinetics of small molecule inhibitors. In this review, we summarized studies from various types of cancer that implicate DYRK1A in their pathogenesis and persistence. Additional studies are needed to validate many of the cell-specific findings; however, the emerging importance of DYRK1A in cancer biology warrants the ongoing development of novel, selective, and clinically efficacious inhibitors.

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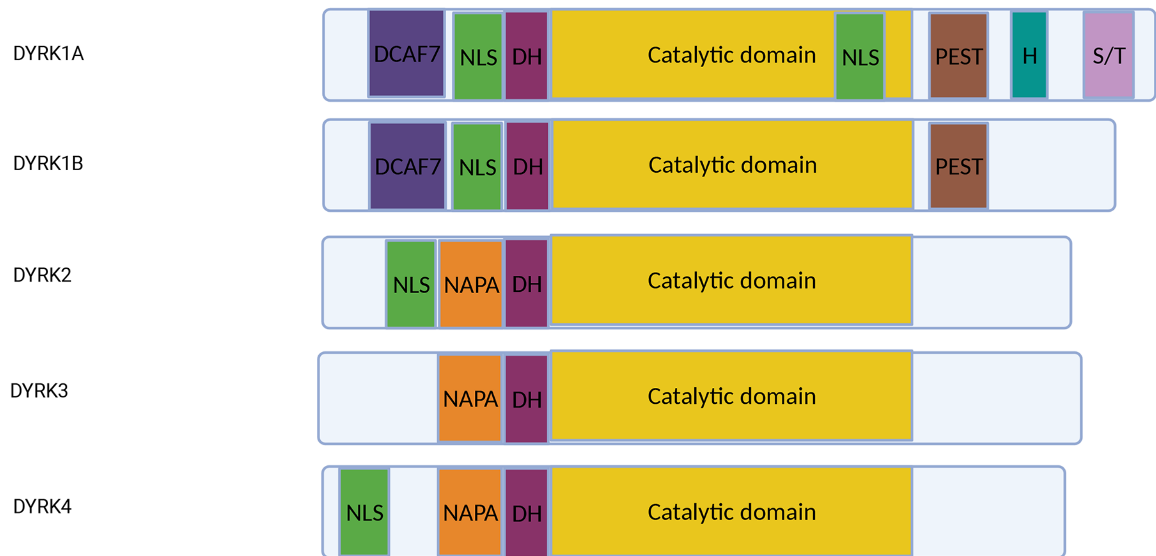

Figure 1: Domain composition of the DYRK proteins.

DYRK1 contains a DCAF7 binding domain, a nuclear localization site (NLS) at the N-terminus, a DYRK homology box (DH), and a proline, glutamate, serine, threonine (PEST) region. DYRK1A contains a second NLS within the catalytic domain, a histidine repeat (H), and serine/threonine (S/T) repeats near the C-terminus. DYRK2, DYRK3, and DYRK4 contain a NAPA domain, DH, and catalytic domain. DYRK2 and DYRK4 also have an N-terminus NLS.

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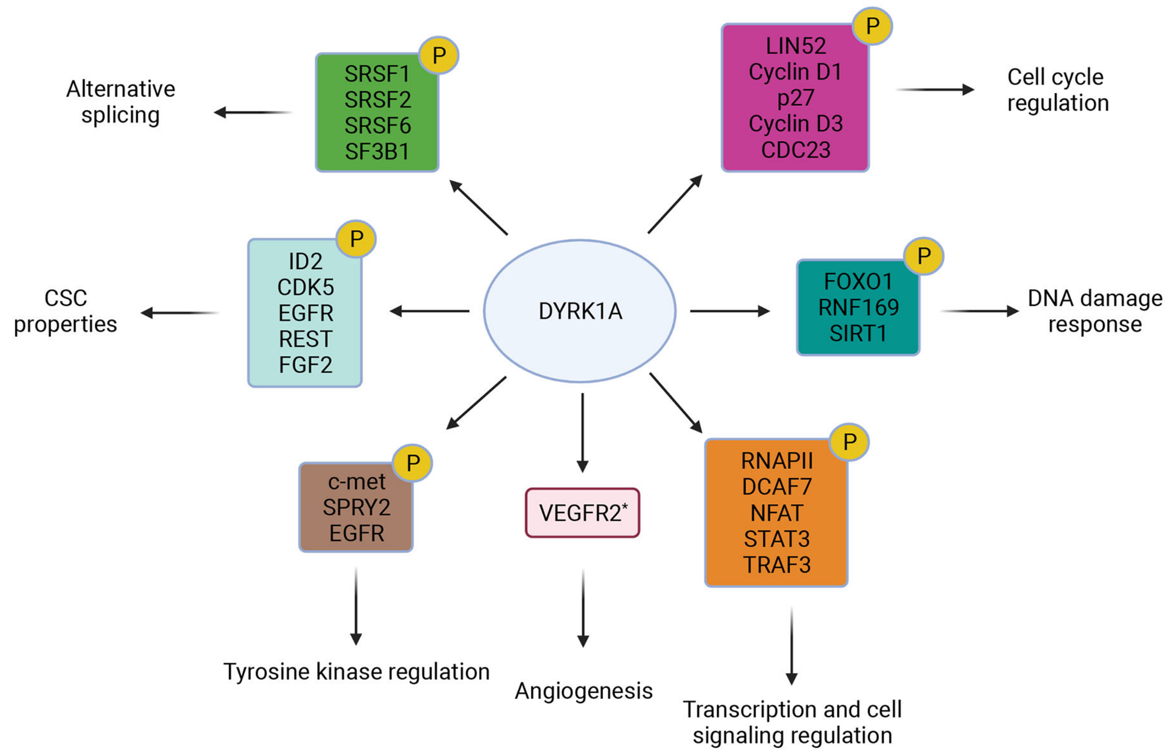

Figure 2: Known DYRK1A substrates.

Targets of DYRK1A include proteins involved in cell cycle regulation, DNA damage response, transcription and cell signaling regulation, angiogenesis, tyrosine kinase regulation, cancer stem cell (CSC) properties, and alternative splicing.

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Table 1.

Summary of the role of DYRK1A in different cancers.

Cancer	Role	Signaling Pathway	References
DS-AMKL	tumor-promoting	NFAT	(61)
ALL	tumor-promoting	FOXO1, STAT3	(46)
AML	tumor-suppressing	c-Myc	(125)
Glioblastoma	both	REST, RNA Polymerase II, EGFR, ID2, cyclin B	(21, 53, 82, 85, 126)
Neuroblastoma	tumor-promoting	p27 and cyclin D1	(41)
PDAC	tumor-promoting	c-MET	(80)
Ovarian	tumor-promoting	MuvB, DREAM	(39)
NSCLC	tumor-promoting	STAT3, EGFR, c-MET, Mcl-1	(75, 127)
Bladder	tumor-promoting	FGF2	(128)
Osteosarcoma	both	DREAM, SIRT1	(38, 52)
Cervical	tumor-suppressing	RNF169, 53BP1	(49)
HNSCC	tumor-promoting	FGF2, FOXO3A	(88, 129)
Epithelial cancer in individuals with DS	tumor-suppressing	NFAT	(59)

DS-AMKL = Down syndrome-acute megakaryoblastic leukemia; PDAC = pancreatic ductal adenocarcinoma; NSCLC = non-small cell lung cancer; HNSCC = head and neck squamous cell carcinoma.

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Table 2.

DYRK1A inhibitors described in cancer studies

DYRK1A Inhibitors	Class of compound	Cancer/Disease tested in	Natural/ Synthetic	References
harmine	β-carboline	*In vitro: colon, gastric, pancreatic, lung, liver, breast ovarian, glioblastoma; In vivo: glioma, HNSCC*	natural	(82, 129, 130)
L41	Leucettine	*In vitro: glioblastoma*	natural	(43)
licocoumarone	flavonoid	*In vitro: PDAC*	natural	(131)
EGCG	Polyphenol	*Clinical trials: colon cancer and prostate cancer*	natural	(132, 133)
Lamerallins	Chromenoindole	*In vitro: leukemia, prostate, melanoma, colon, ovarian, renal, glioma, breast, NSCLC*	synthetic	(134, 135)
INDY	benzothiazol	*In vitro: ovarian, glioblastoma*	synthetic	(39, 82)
Meriolins	Pyrimidinylindol/azaindol	*In vitro: glioma*	synthetic	(136)
Meridianins	Pyrimidinylindol/azaindol	*In vitro: breast, cervical, ovarian leukemia, HNSCC*	synthetic	(137–139)
EHT 1610	Thiazolo[5,4-f]quinazoline	*In vitro/in vivo: B-ALL*	synthetic	(46)
EHT 5372	Thiazolo[5,4-f]quinazoline	*In vitro: pancreatic cancer*	synthetic	(108)
FC 162	Thiazolo[5,4-f]quinazoline	*In vitro: neuroblastoma*	synthetic	(105)
pyrido[3,4-g]quinazoline derivatives	pyrido[3,4-g]quinazoline	*In vitro: colon, breast, neuroblastoma, osteosarcoma*	synthetic	(140)
AnnH-75	β-carboline	*In vitro: cervical cancer, neuroblastoma*	synthetic	(141)
Compound 34	pyrrolopyrimidine	*In vivo: glioblastoma* *In vitro: osteosarcoma*	synthetic	(120)