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Dual-specificity tyrosine-regulated kinases (DYRKs) and cancer

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ABSTRACT

Dual-specificity tyrosine phosphorylation-regulated kinase (DYRK) belongs to the CMGC group of kinases that are named after cyclin-dependent kinases (CDKs), mitogen-activated protein kinases (MAPKs), glycogen synthase kinases (GSKs), and CDC-like kinases (CLKs). DYRK-related kinases comprise a novel subfamily of protein kinases with unique structural, biochemical, and enzymatic features. In humans, DYRKs phosphorylate a set of proteins and play a critical role in apoptosis, DNA damage repair, cell proliferation, survival, and development. Dysregulation of DYRK protein kinases have been associated with cancer biology. In recent years, several studies have reported some kinase inhibitors affecting cancer development and progression, making them potential therapeutic drugs. However, challenges remain in understanding the molecular mechanisms and roles of each member of the DYRK family in cancer initiation and progression. In this review, we will highlight the importance of DYRK kinases in cancer biology.

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Background

Cancer is an abnormal growth of cells. Cancer cells have mutations that lead to dysregulated expression of oncogenes and tumor suppressor genes, the results of these changes altering the expression of hundreds of genes [1-3]. The proto-oncogene c-Src is the first cancer gene identified to encode a protein kinase [4]. In human cells, 538 protein kinases have been identified [5]. Based on the sequence homology of their catalytic domains, these protein kinases are classified into several groups [6]. Dual-specificity tyrosine phosphorylation-regulated kinases (DYRKs) are a subfamily of the CMGC kinase group that encompasses cyclin-dependent kinases (CDKs), mitogen-activated protein kinases (MAPKs), glycogen synthase kinases (GSKs), and CDK-like kinases(CLKs), as well as tyrosine kinase gene v-ros cross hybridizing kinases (RCKs) [6]. The extended DYRK family members are classified into three subfamilies: Dual specificity (DYRK) kinases, pre-messenger RNA processing protein 4 kinases (PRP4s), and homeodomain-interacting protein kinases (HIPKs) [6]. The DYRK subfamily is clustered into two classes (Class I and Class II) with five members in humans. Class I DYRKs include DYRK1A and DYRK1B (also known as Mirk from mini brain-related kinase), and Class II has DYRK2, DYRK3, and DYRK4.

The DYRK members are autophosphorylated on a tyrosine residue to reach full kinase activities [7, 8] and play key roles in signaling pathways that control cell survival, differentiation, cell death, embryonic neurogenesis, development processes [9, 10], and cancer biology [11]. Regarding DYRK involvement in the regulation of tumorigenic processes, several studies have reported alterations in the expression of DYRK genes in tumor samples and have revealed DYRK-dependent mechanisms that contribute to tumor initiation and progression. However, challenges remain, including DYRK kinase inhibitors, clinical implications, and therapeutic opportunities. This review will highlight the importance of DYRK kinases in their involvement in signaling pathways and cancer biology.

DYRK kinase subfamily

DYRK-related kinases compose a distinct family of protein kinases defined by the structural similarity of their kinase domains and their capability to autophosphorylate on tyrosine residues. Autophosphorylation of DYRKs on tyrosine is a one-off event that occurs during translation and induces kinase activation [12, 13] The members of the DYRK family have unrelated sequences outside the catalytic kinase domain (DH-box, Dyrk homology box), and differ in their tissue distribution, substrate specificity, and subcellular localization [14]. Class I DYRKs contain a functional, bipartite nuclear localization signal (NLS) at the N-terminus to the DH-box, and a proline-, glutamic acid-, serine-, and threonine-rich (PEST) at the C-terminus which is typically found in proteins that are targeted for degradation. Class I also contains a histidine-rich region in the C terminus [11, 15]. Class II includes a conserved kinase domain and adjacent N-terminal autophosphorylation accessory region (NAPA) domain to the DH box but not a PEST domain at the C-terminus (Figure 1) that is essential for autophosphorylation of the activation loop tyrosine [16].

The kinase structural domain of DYRK1A contains an N-terminal lobe (N-lobe) with five antiparallel β-strands, a conserved regulatory αC helix, and a larger C-terminal lobe (C-lobe) [17]. DYRK1A and DYRK1B are closely related and highly expressed in human tissues [11], and both are characterized as negative regulators of the cell cycle and are involved in cell survival, growth arrest, and differentiation [18, 19]. The mammalian mini-brain (MNB) ortholog DYRK1A plays a key role in the MNB-like phenotype and aberrant retinal development [20, 21], which indicates a conserved mechanism for the normal development of the central nervous system in mammals [16]. Moreover, DYRK1A protein kinase has a nonredundant vital role in the maintenance of adult brain neuronal activities by regulating transcription factor, nuclear factor of activated T cells (NFAT) [9], and cyclin AMP response element-binding protein (CREB) [22]. DYRK1A and DYRK3-specific runs of histidine residues participate in phase-separated subcellular compartments [23]. DYRK1B has been illustrated as a negative regulator of the cell cycle and encodes a dual-specificity serine/threonine (S/T) protein kinase with roles in cell survival and differentiation [24, 25]. In addition, the kinase activity of DYRK1B attenuates DNA double-strand breaks (DSBs)-induced gene silencing and leads to compromised DNA damage repair that coordinates DSB repair on transcribed chromatin [26]. DYRK2 phosphorylates NFATc and regulates calcium signaling, resulting in NFATc inactivation through cytoplasmic sequestration [9, 27]. Recent studies have shown that DYRK2 is a novel mammalian ciliogenesis-related protein kinase that plays an important role in regulating Hedgehog (Hh) signaling in the control of ciliogenesis [28]. DYRK2

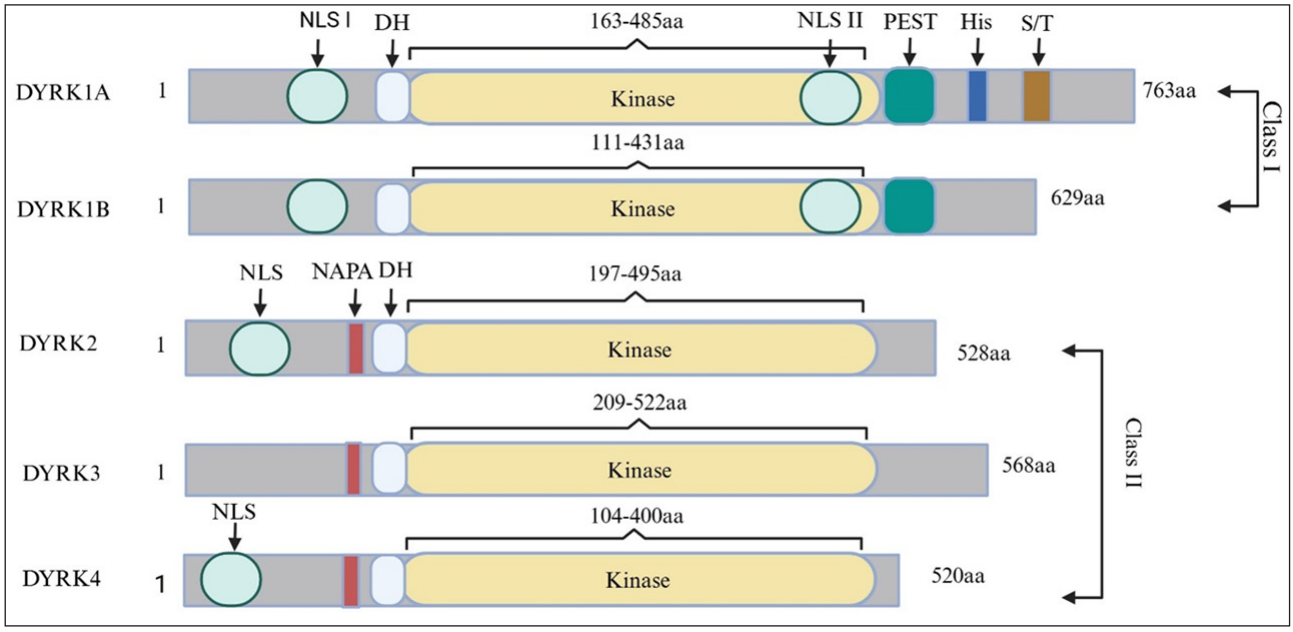

Figure 1: Schematic representation of the mammalian family of DYRKs, indicating their phylogenic relationships, degree of homology, and protein domains. NLS: nuclear localization; DH: DYRK homology; PEST: proline-, glutamic acid-, serine-, and threonine-rich; His: histidine; S/T: serine/threonine; aa: amino acid. Image created in BioRender. Moududee, S. (2024) https://BioRender.com/k39x947.

and DYRK3 are closely related and encoded by paralogous genes that originate from gene duplication [29]. DYRK3 is localized to stress granules (SG) and regulates a cyclic partitioning mechanism between SG and cytosol through its kinase activity [30]. DYRK1A, DYRK2, and DYRK4 differ in their substrate specificities whereas DYRK2 and DYRK4 are less biased than DYRK1A. DYRK4 is widely expressed in all human tissues, unlike its rat and mouse orthologues that are predominantly expressed in the testis [31]. In neurons, DYRK2, DYRK3, and DYRK4 are mostly localized in the cytosolic portion of cell bodies, with DYRK2 seen in the dendrites and part of the axon and DYRK3 and DYRK4 mainly confined to the dendrites; in contrast, DYRK1A is mainly localized to the nucleus [32]. Taken altogether, the structural differences and subcellular localizations of DYRKs may determine their differential functions in the cells.

DYRKs in Cancer

Protein phosphorylation is one of the most significant mechanisms for signal transduction between cells and within cells. DYRK phosphorylation can influence a broad range of cellular processes including transcription, apoptosis, cell cycle progression, cell motility, metabolism, cell survival, and differentiation, which play important roles in human diseases including various cancers. DYRK family members have been linked to cancer biology as their expression is different between normal and tumor tissues and many DYRK substrate proteins are key players in cancer biology [11]. In this section, we will discuss the involvement of each member of the DYRK family in cancer.

DYRK1A

The gene encoding DYRK1A is highly conserved and located on chromosome 21 in the Down syndrome critical region (DSCR) [33]. Previous studies have illustrated that individuals with Down syndrome show a markedly reduced incidence of solid tumors [34] and a considerably lower incidence of cancer-associated mortality [35]. DYRK1A is a pleiotropic kinase that phosphorylates proteins that play crucial roles in angiogenesis, DNA damage repair, cell cycle regulation, cancer stem cell properties, transcription, and cell signaling regulation [36] (Figure 2). DSCR1 is located in the Down syndrome critical region

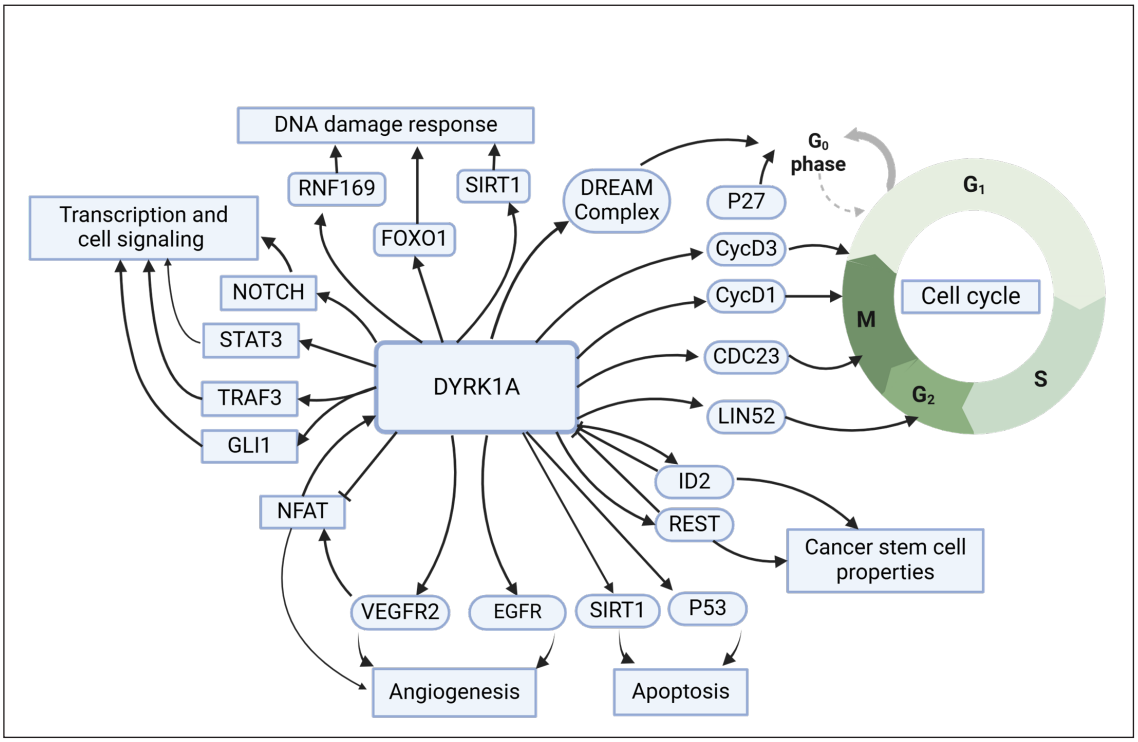

Figure 2: An overview of interactions between DYRK1A and proteins involved in a variety of cellular processes. RNF169: Ring finger protein 169; FOXO1: Forkhead box protein 1; SIRT1: silent information regulator sirtuin 1; NOTCH: neurogenic locus notch homolog protein; STAT3: signal transducer and activator of transcription 3; TRAF3: TNF receptor-associated factor; GLI1: glioma-associated oncogene 1; NFAT: nuclear factor of activated T-cells; VEGFR2: Vascular endothelial growth factor receptor 2; EGFR: epidermal growth factor receptor; p53: tumor protein 53; REST: RE1-silencing factor; ID2: inhibitor of DNA Binding 2; LIN52: protein lin-52 homolog; CDC23: Cell division cycle 23; CycD1: cyclin D1; CycD3: cyclin D3; DREAM: dimerization partner (DP), retinoblastoma (RB)-like, E2F and MuvB complex. Image created in BioRender. Moududee, S. (2024) https://BioRender.com/k39x947.

and coordinates with DYRK1A to reduce angiogenesis through vascular endothelial growth factor 2 (VEGF2)-dependent signaling and the downstream nuclear factor of activated T cells (NFAT)-dependent transcriptional response in endothelial cells [9, 37]. DYRK1A contributes to acute megakaryoblast leukemia (AMKL) development through NFAT signaling [38]. The signal transducer and activator of transcription 3 (STAT3) is a DYRK1A substrate that regulates tumor progression [39, 40] and astrogliogenesis [41]. STAT3 is activated in solid tumors such as lung, prostate, breast, head, neck, gastric, colorectal, hepatocellular, and brain cancers [42]. The inhibition of DYRK1A diminishes STAT3 activities and proliferation of non-small cell lung cancer (NSCLC) cells due to impaired EGFR signaling [43].

Glioma-associated oncogene 1 (GLI1, officially named GLI Family Zinc Finger 1) is an oncogenic transcription factor whose nuclear translocation and functional activity are regulated through phosphorylation by DYRK1A. GLI1 is the effector of Sonic Hedgehog (SHH) signaling that regulates tumor growth and cell survival as well as metastasis [44]. Moreover, the NOTCH pathway has appeared as an oncogenic pathway in solid tumors and blood cancers [45]. On the other hand, it has also been revealed that the NOTCH pathway plays a role as a tumor suppressor in myeloid malignancies [46]. These findings suggest that the NOTCH pathway may have both positive and negative impacts on tumor growth and cell survival. The RE1-silencing factor (REST) is like NOTCH and has been identified as a cancer-related gene in medulloblastoma [47, 48], characterized as an oncogene in neuroblastoma (NB), a common extracranial solid tumor in children [49], and glioblastoma (GBM) that is in the adult brain [50, 51]. Therefore, DYRK1A has diverse, non-redundant roles in cancer biology, which may be a potential target in developing new strategies against cancers.

DYRK1B

DYRK1B is also named Minibrain-related kinase (Mirk). DYRK1B's functions have been well characterized. DYRK1B plays a vital role in muscle differentiation through regulatory effects on transcription, growth arrest, myogenesis, cell cycle progression, motility, and cell survival [25]. Thus, we will discuss the protumorigenic roles of DYRK1B in cancer, which mostly involve prosurvival signaling pathways (Figure 3). DYRK1B kinase is a potential pharmacological target in cancer since it is overexpressed in several

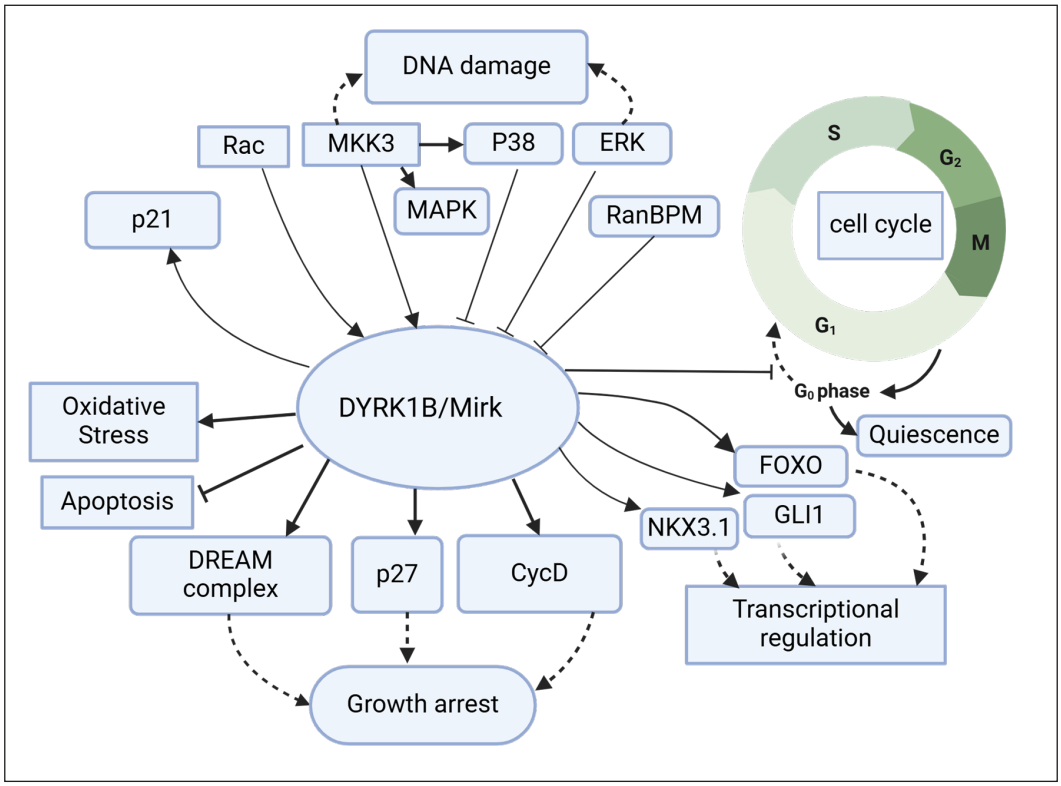

Figure 3: A graphical representation of the interactions between DYRK1B/Mirk and a variety of biological processes. MKK3: mitogen-activated protein kinase (MAPK) kinase 3; Rac: RAS-related C3 botulinum toxin substrate; ERK: extracellular signal-regulated kinase; RanBPM: Ran-binding protein M. CycD: Cyclin D; FOXO: Forkhead box protein; GLI1: glioma-associated oncogene 1. Image created in BioRender. Moududee, S. (2024) https://BioRender.com/k39x947.

types of solid tumors and cancer cell lines, including rhabdomyosarcoma [25], ovarian cancer [52], non-small cell lung carcinoma [53], breast cancer [54], prostate cancer, colon cancer [55, 56], and pancreatic ductal adenocarcinoma [57, 58], and its overexpression is correlated with patients' poor prognosis.

DYRK1B acts as a negative cell cycle regulator to maintain the survival of quiescent cancer cells [3, 59] and as a tumor cell survival factor conferring resistance to chemotherapies by counteracting the G0 / G1–S phase transition [60]. DYRK1B maintains the S phase checkpoint by stabilizing the cyclin-dependent kinase (CDK) inhibitor and induces the degradation of cyclin D [3], respectively. Additionally, the mammalian dimerization partner (DP), retinoblastoma (RB)-like, E2F and MuvB (DREAM) complex represses cell cycle-dependent genes during quiescence complex that represses cell cycle gene expression in G0-arrested cells [3, 19]. The regulation of the cell cycle by DYRK1B is mediated through cyclin D phosphorylation [61-63], suggesting that cancer cells require active Mirk/DYRK1B to maintain quiescent status that is less sensitive to chemotherapy and radiotherapy [64]. In this regard, pharmacological inhibition of DYRK1B may be a promising therapeutic approach to sensitize cancer cells to chemotherapy and radiotherapy.

Inhibition or depletion of DYRK1B has been shown to exaggerate DNA damage and apoptosis caused by chemotherapeutic drugs that target proliferating cells [65-68] in cancer cell lines of various tumor origins [69, 70]. Depletion of DYRK1B increases the nuclear translocation of Forkhead box protein O (FOXO) and enhances the apoptosis of ovarian cancer cells [52]. The functional interaction of DYRK1B and oncogenic transcription factor glioma-associated oncogene family zinc finger 1 (GLI1) significantly reduces *in vivo* tumor growth of GLI1-dependent pancreatic cancer cell lines [71]. In addition, DYRK1B has been reported to target the tumor suppressor NKX3.1 for proteasomal degradation in prostate cancer cell [72]. DYRK1B inhibition in prostate cancer can increase the NKX3.1 suppressor protein level besides its impact on cell cycle regulators [3]. However, it remains elusive to understand its mechanism fully. DYRK1B kinase is active in pancreatic and rhabdomyosarcoma cancer cells through oncogenic mitogen-activated protein kinase 3 (MKK3) signaling pathway [25, 57, 73]. In addition, MKK3 activates p38 in response to stress signals induced by DNA damage [73]. In conclusion, DYRK1B may be a potential pharmacological target in cancer therapy.

DYRK2

DYRK2 has been found in all eukaryotes, and surprisingly across all orthologues, the conserved function of DYRK2 is to regulate cell division and tissue development [74, 75]. Over the past two decades, many studies have found that the substrates of DYRK2 are involved in cell growth, cell survival, cell proliferation, development, gene transcription, and proteasomal regulation [24, 76, 77]. The role of DYRK2 in cancer is the focus of this review.

DYRK2 plays diverse roles as a tumor suppressor and an oncogene in different cancers such as breast, liver, colorectal, ovarian, gastric, lung, and prostate cancers, as well as in chronic myeloid leukemia [76, 78] (Figure 4). Yoshida et al have reviewed the tumor suppressor role of DYRK2 in different cancers with antitumorigenic functions involving apoptosis, cell cycle regulation, cancer stemness, epithelial-to-mesenchymal transition (EMT), and metastasis [79]. DYRK2 suppresses cancer cell proliferation and invasion by regulating cyclin-dependent kinase 14 (CDK14) expression [80]. Previous studies have reported that CDK14 is an oncogene [81-84], and upregulated expression of CDK14 promotes tumor cell proliferation, migration, and invasion in breast cancer [80, 81]. To elucidate the function of DYRK2 as an oncogene, some oncogenic substrates have been reported such as 26S proteasome [74, 85, 86], p53 [27, 87], Heat shock factor 1 (HSF1) [27], c-Myc [88], Seven in absentia homolog 2 (SIAH2) [89], and NOTCH1 [90]. DYRK2 phosphorylates and activates 26S proteasome and HSF1, thereby stimulating the proteotoxic stress pathway during tumorigenesis in breast cancer [78]. Cancer cells are exposed to proteotoxic stress by increasing protein folding capacity that is controlled by HSF1 or expanding the misfolded/aggregated protein degradation through 26S proteasome [91, 92]. DYRK2 phosphorylates the regulatory particle 3 (Rpt3) subunit on the ATPase ring of the 19S subunit of the proteasome on a conserved Thr25 site, leading to enhanced substrate translocation and degradation [74]. Expression of DYRK2 is inversely associated with Snail expression but positively associated with E-cadherin expression, hence DYRK2 regulates Snail and promotes epithelial-mesenchymal transition (EMT) to drive invasion in human breast cancer [93]. Ectopic expression of DYRK2 phosphorylates mTOR at Thr631, leading to ubiquitination and degradation [94]. The correlation between DYRK2 and mTOR regulates the sensitivity to Everolimus (an mTOR inhibitor) in hormone

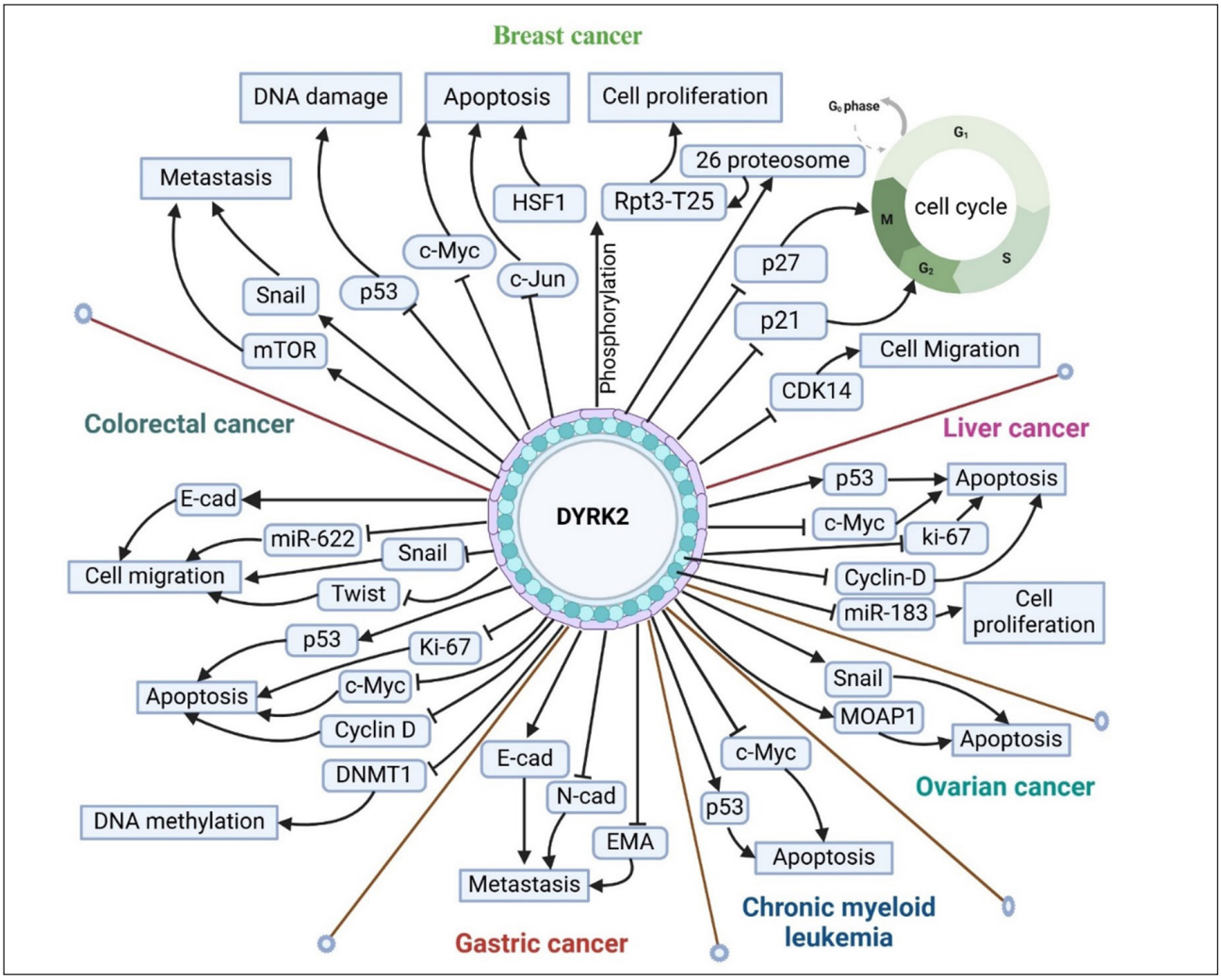

Figure 4: Overview of the roles of DYRK2 in a variety of cancers. HSF1: heat shock factor 1; mTOR: mammalian target of rapamycin; miR622: microRNA 622; E-cad: E-Cadherin; N-cad: neural cadherin; MOAP1: modulator of apoptosis 1, miR183: microRNA 183; CDK14: cyclin dependent kinase 14; Rpt3-T25: regulatory particle 3-T25; ki-67: kiel-67; CycD: Cyclin D; DNMT1: DNA methylation. Image created in BioRender. Moududee, S. (2024) https://BioRender.com/k39x947.

receptor-positive breast cancer [94]. As detailed in a previous review article, DYRK2 may induce apoptosis through phosphorylating c-Jun, c-Myc, and HSF1, inhibit cell stemness by suppressing Kruppel-like factor 4 (KLF4) and telomerase reverse transcriptase (TERT) expression via androgen receptor (AR), and reduce cell proliferation via suppression of CDK14 expression, as well as suppress EMT, invasion, and metastasis through phosphorylation of Snail and induction of mTOR degradation [95].

Colorectal cancer is one of the most common malignant diseases and a leading cause of cancer-related death worldwide [96]. The role of DYRK2 in colorectal cancer has been investigated in cell lines, tissue samples, and xenograft mouse models [28]. DYRK2 phosphorylates p53 to regulate apoptotic cell death in response to DNA damage [27, 79]. Previous studies have shown that DYRK2-mediated phosphorylation initiates the degradation of several proteins via the ubiquitin-proteasome system. Interestingly, DYRK2 functions as a scaffold for the E3 ubiquitin ligase complex containing E3 isolated by the differential display (EDD), DNA damage-binding protein 1 (DDB1), and Vpr binding protein (VPRBP), and DYRK2–EDVP E3 ligase complex. Meanwhile, the E3 ubiquitin ligase complex has a crucial function in regulating normal mitotic progression because overexpression of both DYRK2 and EDD [97, 98] is frequently reported in cancers [2]. Overexpression of DYRK2 suppresses c-Jun, c-Myc, Ki-67, and Cyclin-D expression, thus inhibiting cell growth, cell migration, invasion, and metastasis of colorectal cancer [96, 99]. DYRK2 plays an important role in epithelial-mesenchymal transition (EMT) by degrading Snail and stabilizing E-

cadherin, leading to inhibition of cell migration and invasion [96]. DYRK2 expression is correlated with an EMT transcription factor TWIST, DNA methylation (DNMT1), and a tumor-related gene (miR-622) in colorectal cancer samples and cell lines [100, 101].

The functional roles of DYRK2 in gastric, leukemia, ovarian, liver, and prostate cancer have also been investigated in patient tissue samples, cell lines, and xenograft mouse models [28]. Taken together, these reports suggest that DYRK2 may be a tumor suppressor or oncogene dependent on the cancer type, which can be targeted differentially according to its role in each type of cancer.

DYRK3 & DYRK4

The roles of DYRK3 and DYRK4 in cancer have not been well studied compared to the other DYRKs [11]. A limited number of studies have revealed the important roles of DYRK3 and DYRK4 in tumorigenesis.

Analysis of DYRK3 substrates has led to identifying consensus phosphorylation sequences for DYRK proteins [102]. DYRK3 promotes cell survival through phosphorylation and activation of silent information regulator sirtuin 1 (SIRT1), an NAD^+-dependent protein deacetylase that has potential in various physiological processes including energy metabolism and stress response. Knockdown of endogenous DYRK1A and DYRK3 leads to hypophosphorylation of SIRT1 and increased acetylation levels of p53 to regulate p53-mediated apoptotic response to genotoxic stress [103]. In organisms across the eukaryotic kingdom, DYRK3 is linked to cellular stress responses, ranging from genotoxic stress, irradiation, nutrient starvation, and osmotic stress [29, 104, 105]. DYRK3 regulates the stability of P-granule-like structures and couples stress granule dissolution to the mechanistic target of rapamycin complex 1 (mTORC1) signaling [30] (Figure 5). Moreover, DYRK3 regulates the phase transition of membrane-less organelles in mitosis [106]. It presents a cyclic partitioning mechanism between stress granules and the cytosol via a low-complexity domain in its N terminus and its kinase activity [30]. A recent study has reported that DYRK3 may influence the formation of plasma membrane-associated platforms (PMAPs) by regulating Liprin-α1's ability to assemble the protein network that promotes cell motility at the edge of the cell, affecting the formation of PMAPs and the formation and turnover of adhesions at the protruding cell edge [107].

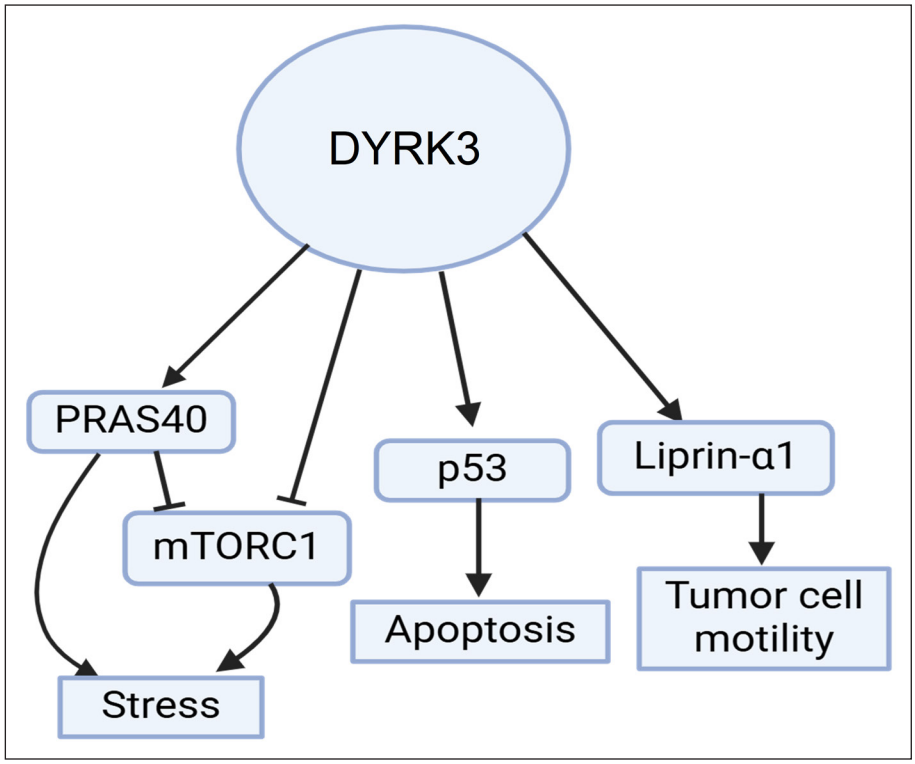

Figure 5: An overview of the interactions between DYRK3 and proteins involved in several biological processes. PRAS40: proline-rich Akt substrate of 40; mTORC1: mammalian target of rapamycin complex 1, Liprin-α1: Liprin-alpha1. Image created in BioRender. Moududee, S. (2024) https://BioRender.com/k39x947.

A few studies have found DYRK3's roles in specific types of tumors. One study has revealed that DYRK3 inhibits hepatocellular carcinoma (HCC) [108], whereas another study has shown that DYRK3 was upregulated in neuroblastoma patients with poor prognosis [109]. DYRK3 may be linked to the aggressiveness of glioblastoma [110, 111], and downregulation of DYRK3 impairs glioblastoma cell migration and invasion [112]. A recent study has shown that DYRK3 is a tumor-promoting oncogene in serous ovarian cancer (SOC) as DYRK3 knockdown inhibits cell viability, invasion, and in vivo tumor growth [113]. Overall, DYRK3's roles in cancer are complicated and cancer-type dependent.

DYRK4 is the fourth member of the DYRK subfamily, which has not been well studied in cancer. One study has found that phosphorylation of the second tyrosine residue within the activation loop appears to have the potential for the full activity of DYRK4 [31]. DYRK4 exhibits different substrate specificity, unlike other members of the DYRK family, with 24 out of 30 peptide substrates containing a serine/threonine residue followed by a proline, indicating that DYRK4 may be characterized as a proline-directed kinase [31]. DNA methylation is one of the most common epigenetic modifications and plays a potential role in carcinogenesis [114]. A recent study has revealed an association between DYRK4 hypomethylation in peripheral blood and an increased risk of lung cancer (LC), which suggests the feasibility of blood-based DNA methylation as a new biomarker for the detection of LC [115]. The mechanism and functional implications underlying this association between DYRK4, and LC need further investigation. Another study has reported that overexpression of a neoplastic chimerical transcript RAD51AP1-DYRK4 is associated with luminal B breast cancers (7–17.5 %), and expression of RAD51AP1-DYRK4 is tumor-specific and enriched in estrogen receptor-positive (ER+) luminal B breast tumors (7–18%) compared to luminal A tumors (3–4%) [116]. However, the pathological role of RAD51AP-DYRK4 in luminal B breast cancer remains unclear. Future studies will be needed to pinpoint the mechanisms engaged by RAD51AP1-DYRK4 to endow breast cancer cells.

Conclusion

Current literature reports indicate that DYRKs are a new class of 'kinase of interest' in human diseases including cancer. However, the roles of DYRKs in cancer have not been fully elucidated, although there are many findings from studying DYRK expression in cancer cell lines, tumor tissues, and xenografted mouse models. DYRKs have been shown to play tumor-suppressor roles or oncogenic roles, depending on the specific DYRK members and types of cancer. More studies are needed to understand the physiological and pathological functions of DYRK family members in normal and malignant cells. This knowledge will help develop DYRK inhibitors that may have potential in cancer treatment. However, many challenges will be encountered as DYRKs appear to be activated when they are translated, thus lacking an obvious upstream kinase to be targeted. Targeting DYRKs per se or their binding to their substrates may be feasible as shown by a limited number of DYRK inhibitors. Developing a highly selective inhibitor against a specific DYRK member is another challenge, which must be considered as the roles of DYRKs are different.

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