

World Journal of *Stem Cells*

World J Stem Cells 2020 December 26; 12(12): 1439-1690



REVIEW

- 1439 Brain tumors: Cancer stem-like cells interact with tumor microenvironment
Liu HL, Wang YN, Feng SY
- 1455 Effect of metformin on stem cells: Molecular mechanism and clinical prospect
Jiang LL, Liu L
- 1474 Novel insights for improving the therapeutic safety and efficiency of mesenchymal stromal cells
Najar M, Martel-Pelletier J, Pelletier JP, Fahmi H
- 1492 Noninvasive *in vivo* cell tracking using molecular imaging: A useful tool for developing mesenchymal stem cell-based cancer treatment
Rajendran RL, Jogalekar MP, Gangadaran P, Ahn BC
- 1511 Prospects for the therapeutic development of umbilical cord blood-derived mesenchymal stem cells
Um S, Ha J, Choi SJ, Oh W, Jin HJ
- 1529 Mesenchymal stem cells secretome: The cornerstone of cell-free regenerative medicine
González-González A, García-Sánchez D, Dotta M, Rodríguez-Rey JC, Pérez-Campo FM
- 1553 Minibrain-related kinase/dual-specificity tyrosine-regulated kinase 1B implication in stem/cancer stem cells biology
Kokkorakis N, Gaitanou M

ORIGINAL ARTICLE**Basic Study**

- 1576 Acupuncture accelerates neural regeneration and synaptophysin production after neural stem cells transplantation in mice
Zhao L, Liu JW, Kan BH, Shi HY, Yang LP, Liu XY
- 1591 Spinal cord injury regeneration using autologous bone marrow-derived neurocytes and rat embryonic stem cells: A comparative study in rats
Sadat-Ali M, Al-Dakheel DA, Ahmed A, Al-Turki HA, Al-Omran AS, Acharya S, Al-Bayat MI
- 1603 6-gingerol protects nucleus pulposus-derived mesenchymal stem cells from oxidative injury by activating autophagy
Nan LP, Wang F, Liu Y, Wu Z, Feng XM, Liu JJ, Zhang L
- 1623 Stem cells from human exfoliated deciduous teeth ameliorate concanavalin A-induced autoimmune hepatitis by protecting hepatocytes from apoptosis
Zhou YK, Zhu LS, Huang HM, Cui SJ, Zhang T, Zhou YH, Yang RL

- 1640** Influence of donor age on the differentiation and division capacity of human adipose-derived stem cells
Horinouchi CD, Barisón MJ, Robert AW, Kuligovski C, Aguiar AM, Dallagiovanna B
- 1652** Umbilical cord-derived mesenchymal stem cells preconditioned with isorhamnetin: potential therapy for burn wounds
Aslam S, Khan I, Jameel F, Zaidi MB, Salim A
- 1667** Effects of normobaric cyclic hypoxia exposure on mesenchymal stem-cell differentiation-pilot study on bone parameters in elderly
Camacho-Cardenosa M, Quesada-Gómez JM, Camacho-Cardenosa A, Leal A, Dorado G, Torrecillas-Baena B, Casado-Díaz A

ABOUT COVER

Editorial Board Member of *World Journal of Stem Cells*, Dr. Mohammed Grawish is a Distinguished Professor at Mansoura University and Vice-Dean for Community Services and Environmental Affairs at Delta University for Science and Technology (Egypt). Dr. Grawish received his Bachelor's degree (1990), Master's degree in Oral Biology (1998), and his PhD (2003) from the Faculty of Dentistry, Mansoura University. After, he worked as Lecturer in the Al-Gabl Al-Garby University (2005-2008; Gehrian, Libya) and as Associate Professor in the King Saud University (2011-2013; Riyadh, Saudi Arabia). His ongoing research interests focus mainly on the appropriate therapeutic use of stem cells in dentistry, the design and characterization of biomaterials as scaffold materials for loading stem cells, and the application of complementary and alternative medicine as an adjunctive treatment to traditional medicine for oral diseases. (L-Editor: Filipodia)

AIMS AND SCOPE

The primary aim of *World Journal of Stem Cells (WJSC, World J Stem Cells)* is to provide scholars and readers from various fields of stem cells with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJSC* publishes articles reporting research results obtained in the field of stem cell biology and regenerative medicine, related to the wide range of stem cells including embryonic stem cells, germline stem cells, tissue-specific stem cells, adult stem cells, mesenchymal stromal cells, induced pluripotent stem cells, embryonal carcinoma stem cells, hemangioblasts, lymphoid progenitor cells, *etc.*

INDEXING/ABSTRACTING

The *WJSC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Biological Abstracts, BIOSIS Previews, PubMed, and PubMed Central. The 2020 Edition of Journal Citation Reports® cites the 2019 impact factor (IF) for *WJSC* as 3.231; IF without journal self cites: 3.128; Ranking: 18 among 29 journals in cell and tissue engineering; Quartile category: Q3; Ranking: 113 among 195 journals in cell biology; and Quartile category: Q3.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yan-Xia Xing; Production Department Director: Yun-Xiaojuan Wu; Editorial Office Director: Ze-Mao Gong.

NAME OF JOURNAL

World Journal of Stem Cells

ISSN

ISSN 1948-0210 (online)

LAUNCH DATE

December 31, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Shengwen Calvin Li, PhD, MPhil., FRSM, Tong Cao, Carlo Ventura

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-0210/editorialboard.htm>

PUBLICATION DATE

December 26, 2020

COPYRIGHT

© 2020 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Minibrain-related kinase/dual-specificity tyrosine-regulated kinase 1B implication in stem/cancer stem cells biology

Nikolaos Kokkorakis, Maria Gaitanou

ORCID number: Nikolaos Kokkorakis 0000-0002-8901-1237; Maria Gaitanou 0000-0002-0239-4467.

Author contributions: Kokkorakis N and Gaitanou M wrote the manuscript; All authors reviewed, edited and approved the final manuscript.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Specialty type: Cell and tissue engineering

Country/Territory of origin: Greece

Peer-review report's scientific

Nikolaos Kokkorakis, Maria Gaitanou, Laboratory of Cellular and Molecular Neurobiology-Stem Cells, Hellenic Pasteur Institute, Athens 11521, Greece

Corresponding author: Maria Gaitanou, BSc, PhD, Research Assistant Professor, Laboratory of Cellular and Molecular Neurobiology-Stem Cells, Hellenic Pasteur Institute, Vas. Sofias 127, Athens 11521, Greece. mgaitanou@pasteur.gr

Abstract

Dual-specificity tyrosine phosphorylation-regulated kinase 1B (DYRK1B), also known as minibrain-related kinase (MIRK) is one of the best functionally studied members of the DYRK kinase family. DYRKs comprise a family of protein kinases that are emerging modulators of signal transduction pathways, cell proliferation and differentiation, survival, and cell motility. DYRKs were found to participate in several signaling pathways critical for development and cell homeostasis. In this review, we focus on the DYRK1B protein kinase from a functional point of view concerning the signaling pathways through which DYRK1B exerts its cell type-dependent function in a positive or negative manner, in development and human diseases. In particular, we focus on the physiological role of DYRK1B in behavior of stem cells in myogenesis, adipogenesis, spermatogenesis and neurogenesis, as well as in its pathological implication in cancer and metabolic syndrome. Thus, understanding of the molecular mechanisms that regulate signaling pathways is of high importance. Recent studies have identified a close regulatory connection between DYRK1B and the hedgehog (HH) signaling pathway. Here, we aim to bring together what is known about the functional integration and cross-talk between DYRK1B and several signaling pathways, such as HH, RAS and PI3K/mTOR/AKT, as well as how this might affect cellular and molecular processes in development, physiology, and pathology. Thus, this review summarizes the major known functions of DYRK1B kinase, as well as the mechanisms by which DYRK1B exerts its functions in development and human diseases focusing on the homeostasis of stem and cancer stem cells.

Key Words: Dual-specificity tyrosine-regulated kinase 1B; Minibrain-related kinase; Stem cells; Cancer stem cells; Quiescence; Cell proliferation/differentiation; Cell survival; Cancer; Hedgehog

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

quality classification

Grade A (Excellent): 0
 Grade B (Very good): B, B
 Grade C (Good): C, C
 Grade D (Fair): D
 Grade E (Poor): 0

Received: July 10, 2020

Peer-review started: July 10, 2020

First decision: September 17, 2020

Revised: September 29, 2020

Accepted: October 15, 2020

Article in press: October 15, 2020

Published online: December 26, 2020

P-Reviewer: Garg M, Grawish M, Li YH, Ventura C

S-Editor: Gao CC

L-Editor: Filipodia

P-Editor: Xing YX



Core Tip: Dual-specificity tyrosine phosphorylation-regulated kinase 1B (DYRK1B), also known as minibrain-related kinase (MIRK) is the well-studied member of the DYRK kinase family. DYRK1B is a key regulator of signaling pathways that control proliferation and differentiation, and is critical for developmental processes and cell homeostasis. In this review, we aim to bring together what is known about the functional integration and cross-talk between DYRK1B and several pathways, such as sonic hedgehog, RAS and PI3K/mTOR/AKT pathways and how this might affect the behavior of stem cells in development and disease, taking into consideration potent therapeutic interventions and approaches.

Citation: Kokkorakis N, Gaitanou M. Minibrain-related kinase/dual-specificity tyrosine-regulated kinase 1B implication in stem/cancer stem cells biology. *World J Stem Cells* 2020; 12(12): 1553-1575

URL: <https://www.wjgnet.com/1948-0210/full/v12/i12/1553.htm>

DOI: <https://dx.doi.org/10.4252/wjsc.v12.i12.1553>

INTRODUCTION

Stem cells have the potential to self-renew and therefore to perpetuate their lineage, to give rise to progeny capable of differentiating into specialized diverse cell types^[1,2] interacting with environmental stimuli in order to maintain the balance between quiescence, proliferation, and restoration^[3,4]. All these properties are comprised in the term “stemness”. Specific stimuli induce the emergence of new stem cells, as cells that maintain the capacity to re-differentiate and return to an earliest state of development^[5-7]. Stem cells can be divided into two broad type categories: embryonic stem cells (ESCs), which are derived from the inner cell mass of the blastocyst and are pluripotent, maintaining the ability to differentiate into any cell type^[8-10] and adult (somatic) stem cells being present at niches in adult tissues^[11], which are multipotent, having the ability to differentiate into a limited number of cell lineages and therefore to enable the healing, growth, and replacement of cells that are lost each day of life^[10].

Although adult stem cells exhibit regenerating properties when participating in tissue homeostasis, cancer stem cells (CSCs) behave as their malignant counterparts. CSCs were first identified in the acute myeloid leukemia^[12,13] and are similar to normal stem cells, which have the ability of self-renewal and differentiation into other cell types^[12,14]. CSCs display stemness during cancer progression and through interaction with their environment^[15,16]. CSCs constitute a subpopulation of tumor bulk and are considered as the primary tumor-initiating cells. Tumor heterogeneity derived from CSCs and their progeny is considered as a major disadvantage of their roles in cancer therapies. However, scientific evidence from studies investigating the biology of CSCs, will open up new perspectives for the development of novel therapeutic interventions and elimination of cancer recurrence. Further studies have demonstrated that CSCs have a key role in resistance to cancer therapies, such as chemotherapy and radiation therapy, and increased risk of metastatic potential^[13,17].

DYRK kinases (for dual-specificity tyrosine-(Y)-phosphorylation-regulated kinases) comprise a family of protein kinases which are key regulators of signal transduction, cell proliferation, survival, and differentiation^[18]. DYRKs belong to the CMGC group of proline-directed serine/threonine kinases that are characterized by their ability to phosphorylate tyrosine, serine and threonine amino acid residues^[19-21]. To acquire their catalytic activity, DYRKs require phosphorylation at the second tyrosine residue of a conserved YxY motif, located at their activation loop; thus, DYRKs activate themselves during their translation by intramolecular auto-phosphorylation^[22]. In particular, a characteristic sequence motif DYRK homology box (known as the DH box), which is located at the N-terminal of the catalytic domain, supports the auto-phosphorylation of the conserved tyrosine during maturation of the catalytic domain^[18,21]. DYRK family members have been found in all eukaryotes and constitute an evolutionarily conserved family of protein kinases, which are key players in the regulation of cell cycle and differentiation, regulation of transcription, protein stability and apoptosis, through the phosphorylation of DYRK recognition sites in several target proteins^[21,23,24]. There are five members within the mammalian DYRK kinase family: Class I (or DYRK1 group), consisting of DYRK1A and DYRK1B; and Class II (or DYRK2 group), consisting of

DYRK2, DYRK3 and DYRK4^[18,21]. Notably, DYRK kinases act as priming kinases, phosphorylating a residue and allowing for additional phosphorylation of a second residue by a subsequent kinase^[21].

DYRK1B (also referred to as MIRK; minibrain-related kinase) is closely related to the *DYRK1A* gene, while *minibrain* (*mnb*) is their orthologous gene in *Drosophila*. The *mnb* gene was named according to the brain phenotype of the mutant flies^[21,25]. Disruption of *mnb* causes abnormal arrangement of neuroblasts in the outer proliferation layers of the larval brain, resulting in adult flies with smaller optic lobes and brain hemispheres, suggesting that *mnb* is required for proper proliferation of neuroblasts during larval development and that it plays an essential role during neurogenesis^[21,25,26]. These morphological alterations in mutant flies are associated with specific behavioral abnormalities in learning, memory, and visual and olfactory tasks^[21,25]. While DYRK1A plays a role in neuronal development^[27-34], DYRK1B has a critical role in skeletal muscle differentiation, in spermatogenesis and in cancer *via* its regulatory effects on cell cycle progression and differentiation, cell survival, motility, and transcription^[21,23,24]. Recently, we revealed a novel role for DYRK1B in neuronal development, as we will discuss below^[35] (Kokkorakis *et al.*, 2020 unpublished data).

Here, we will review DYRK1B physiological and pathological roles and its implication in stem/CSC biology, as well as DYRK1B cross-talk with major signaling pathways and the mechanisms by which DYRK1B exerts its function.

DYRK1B EXPRESSION, INTRACELLULAR LOCALIZATION, AND UPSTREAM REGULATION

DYRK1B is normally expressed at high levels in skeletal muscle and testis with increased relative expression in cardiac muscle and brain compared to other normal tissues^[24,36]. DYRK1B is overexpressed in various solid tumors and cancer cell lines, where it seems to act as a tumor survival factor^[24]. The human DYRK1B gene is located on chromosome 19q13.2, a region often amplified in ovarian and pancreatic cancer^[37-42]. DYRK1B is especially highly expressed in colon carcinoma^[36,43,44], prostate carcinoma^[24,45-47], lung cancer^[45], pancreatic ductal adenocarcinomas^[37,48-52], rhabdomyosarcomas^[53], osteosarcoma^[54], and liposarcoma^[55]. Also, overexpression of DYRK1B has been reported in breast cancer^[56-58], cervical cancer^[59,60], and mela-noma^[61,62].

Leder and colleagues^[63] have characterized three splicing variants of mouse DYRK1B DYRK1B-p65, DYRK1B-p69 and DYRK1B-p75 with discrete expression patterns and enzymatic activities. DYRK1B-p65 and DYRK1B-p69 display similar expression patterns, where the highest expression of both isoforms has been detected in the murine spleen, lung, brain, bladder, stomach, and testis. In contrast, DYRK1B-p75 was observed specifically in skeletal muscle, as well as in the neuronal cell line GT1-7 and in differentiated adipocyte-like 3T3-L1 but not in non-differentiated 3T3-L1 preadipocyte cells^[63].

Notably, DYRK1B-p65 differs from DYRK1B-p69 by the absence of 40 amino acids within its catalytic domain, resulting in a lack of kinase activity^[63]. The amino acid sequence of the DYRK1B kinase domain is 56% identical with the other DYRK family kinases; however, the N- and C-termini are non-conserved^[24]. The functional domains in DYRK1B kinase are the DH box, located at the N-terminus of the catalytic domain and supporting auto-phosphorylation^[26,64,65], a bipartite nuclear localization signal (NLS) located at the non-conserved N-terminus, 11 canonical kinase subdomains followed by a proline, glutamate, serine, threonine (commonly known as PEST) sequence, considered to act as a degradation signal for rapidly metabolized proteins and as a consensus sequence for mitogen-activated protein kinases' (MAPKs) phosphorylation^[24,66].

In agreement, DYRK1B shows a predominant nuclear localization in various cell lines, whereas a major cytosolic staining is observed in adult human muscle fibers, rhabdomyosarcoma, and pancreatic ductal carcinomas^[21,43]. Our group has observed the nuclear localization of DYRK1B in all neuronal lineage precursors, as well as in post-mitotic neurons and glial cells of embryonic and postnatal mouse brain and spinal cord (Kokkorakis *et al.*, 2020 unpublished data). In mouse neuroblastoma Neuro2A cells, when DYRK1B is transiently expressed alone, it is localized into the nucleus, and when it is co-expressed with its interacting partner, the scaffolding protein RanBPM, DYRK1B is relocated and subsequently degraded in the cytoplasm^[35]. It has been proposed that the differential intracellular localization of DYRK1B is associated with its discrete roles, *e.g.*, in the nucleus as a negative regulator of cell cycle progression and in the cytosol as a prosurvival factor^[67-69].

DYRK1B kinase is subjected to a high degree of regulatory control at transcriptional, translational and post-translational level, *via* activating and inactivating phosphorylations that result in DYRK1B subcellular relocalization, protein stability, and in its participation in discrete protein-protein interactions^[24]. The regulation of DYRK1B expression and activity has been studied in myoblasts and in cancer cell lines. In cultured C2C12 myoblasts, mitogen deprivation increased DYRK1B protein levels through transcriptional mechanisms regulated by small Rho GTPases, RhoA and Cdc42, and by Rac1, but not by MyoD or Myf5^[24,70].

Additional studies have shown that DYRK1B is a mitogen-activated protein kinase, down-regulated by activated extracellular signal-regulated kinases (ERKs). It was shown that DYRK1B levels increased 20-fold when ERK activation was blocked by the MEK inhibitor PD98059 in colon carcinoma cell lines. PD98059 inhibitor also activated a DYRK1B promoter construct^[70]. Therefore, DYRK1B induction seems to require not only active Rho proteins but also the inhibition of the MEK1-ERK signaling pathway. In accordance, DYRK1B is strongly up-regulated under conditions of mitogen deprivation, *e.g.*, when insulin-like growth factor-1 (IGF-1) is eliminated in a colon carcinoma culture^[66], also suggesting that DYRK1B is a stress-activated kinase, negatively regulated by the RAS-MEK-ERK pathway^[71] (Figure 1). Moreover, knockdown of DYRK1B by small interfering RNA (commonly referred to as siRNA) performed in human ovarian cancer cell lines, led to up-regulated activation of c-Raf-MEK-ERK1/2 pathway and subsequent changes in cell cycle proteins, such as cyclin D1 and p27^{Kip1}, that are accompanied by increased growth rate and re-entering of cancer cells from the G1/G0 phase into the S phase of the cell cycle^[72]. The cell cycle transition could be blocked by MAPK/ERK inhibitor U0126 in a dose-dependent manner, suggesting that DYRK1B and the MAPK/ERK pathway inhibit each other^[42,72] (Figure 1).

In another study, it was found that DYRK1B competes with the stress-activated MAPK kinase p38 for their common activator, the MAPK kinase MKK3^[71]. DYRK1B is activated *in vivo* by MKK3, while p38 seems to be required for terminal muscle cell differentiation^[70]. C2C12 myoblasts expressing a MKK3 dominant negative failed to fuse into myotubes^[70]. The lack of MKK3 activity, by the usage of a MKK3 dominant negative, resulted in decreased expression of MyoD and myogenin that are transcriptional targets of DYRK1B and in blocked expression of the late differentiation markers troponin T, myosin heavy chain (commonly known as MHC), and the Cdk inhibitor p21^{Cip1}^[70]. In addition, p38 blocks DYRK1B transactivation of the transcription factor HNF1 α ^[24,73]. A possible mechanism concerning the *in vivo* interaction between p38 and DYRK1B was suggested from results of cell cycle synchronization experiments in NIH3T3 cells, where DYRK1B levels fluctuated within the cell cycle, whereas p38 levels remained stable, leading to speculation that endogenous p38 can block DYRK1B function, only when DYRK1B levels are low in S phase and not when DYRK1B levels are elevated during G1/G0 transition^[73] (Figure 1).

DYRK1B KINASE FUNCTIONS

DYRK1B is a multifunctional dual-specificity kinase involved in growth arrest, differentiation, and cell survival. The two major functions of DYRK1B are the G1/G0 transition and the subsequent growth arrest in a quiescent state (G0), as well as the maintenance of cell viability^[42,69,70]. DYRK1B function is implicated in myogenesis, during which myoblasts are differentiated into skeletal muscle cells^[69,70,74]. Moreover, DYRK1B participates in muscle regeneration after injury, promoting the activation of quiescent muscle stem cells, also known as satellite cells^[70]. In addition, DYRK1B is involved in fat cell differentiation, from adult mesenchymal stem cells^[75] to preadipocytes that differentiate into adipocytes during adipogenesis, and is linked to metabolic syndrome^[76]. Furthermore, DYRK1B negatively regulates proliferation of immature male germ cells of the seminiferous epithelium, also called spermatogonial stem cells^[77], during spermatogenesis^[78].

Recently, our studies revealed a novel role for DYRK1B in neurogenesis^[35] (Kokkorakis *et al.*, 2020 unpublished data). We have previously demonstrated that DYRK1B overexpression promotes cell cycle exit and neuronal differentiation in mouse neuroblastoma Neuro2A cells by phosphorylating cyclin D1, followed by its cytoplasmic relocation and its subsequent degradation by the 26S proteasome^[35]. We have also shown that the negative effect of DYRK1B in Neuro2A proliferation is reversed when DYRK1B is co-expressed with its interacting partner, the scaffolding protein RanBPM that inhibits DYRK1B function by facilitating its proteasomal

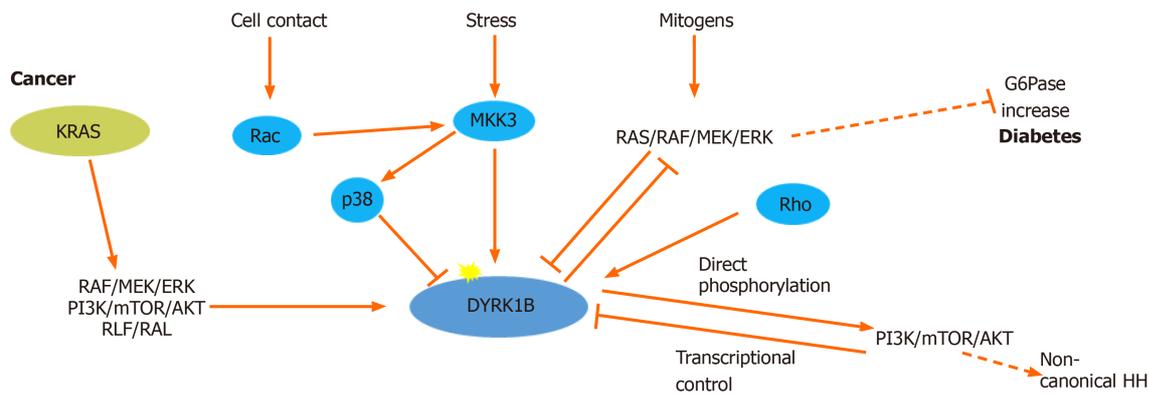


Figure 1 Regulation of dual-specificity tyrosine-regulated kinase 1B expression and activity. Dual-specificity tyrosine-regulated kinase 1B (DYRK1B) expression and activity is regulated at transcriptional, translational and post-translational level. Rho GTPases (RhoA, Cdc42 and Rac1) promote transcriptional up-regulation of DYRK1B, while serum mitogens down-regulate DYRK1B through RAS/RAF/MEK/extracellular signal-regulated kinases (ERK) signaling pathway. Under stress conditions, MKK3 activates DYRK1B and p38, while DYRK1B is physically sequestered and inhibited by p38. In cancer, DYRK1B is involved in a complex crosstalk with hedgehog (HH). Oncogenic mutant RAS (KRAS) initiates the non-canonical HH pathway through the activation of DYRK1B, via an unknown mechanism, employing several RAS effectors, such as: RAF/MEK/ERK, PI3K/AKT and RLF/RAL. DYRK1B enhances non-canonical HH signaling by promoting PI3K/mTOR/AKT signaling. Conversely, activated AKT directly inhibits expression of DYRK1B. In metabolic syndrome, which is accompanied by diabetes, DYRK1B is implicated in glucose homeostasis, promoting the expression of the key gluconeogenic enzyme glucose-6-phosphatase (G6pase), through inhibition of the RAS–RAF–MEK pathway. Dashed lines represent indirect mechanisms and yellow stars represent phosphorylations. ERK: Extracellular signal-regulated kinases.

decay^[35]. In addition, we have demonstrated that the tripartite functional interactions between DYRK1B, RanBPM and the neuronal protein Cend1 (for cell cycle exit and neuronal differentiation 1; also known as BM88) regulate the balance between cellular proliferation and differentiation in Neuro2A cells, suggesting that the three proteins may also play a similar role in cell cycle progression/exit and differentiation of neural stem cells/neural progenitor cells (NSCs/NPCs) during neurogenesis^[35,79]. In agreement, we recently found that DYRK1B is expressed during central nervous system (CNS) development and marks all along the neuronal lineage (Kokkorakis *et al.*, 2020 unpublished data). We have also found that DYRK1B promotes *in vitro* and *in vivo* cell cycle exit and neuronal differentiation in neuronal precursors, suggesting a role in NSCs' differentiation (Kokkorakis *et al.*, 2020 unpublished data).

Notably, excepting its physiological roles, DYRK1B has a significant role in tumorigenesis and cancer progression^[43,52,80], as well as in the maintenance of stemness in CSCs^[81]. Below, we will describe in detail the known functions of DYRK1B kinase in various tissues and cell lines in health and in disease.

DYRK1B mainly acts as a cell cycle regulator

DYRK1B acts as a G0 checkpoint kinase and its levels are highly increased in G0-arrested non-dividing cells, such as serum-starved NIH3T3 fibroblasts^[82] and myoblasts, committing terminal differentiation through cell cycle exit^[70]. In cycling myoblasts, DYRK1B protein levels are very low, whereas they are increased at least 10-fold when myoblasts undergo terminal differentiation and are maintained high in the mature muscle cells^[70]. Moreover, DYRK1B levels are strongly up-regulated in NIH3T3 fibroblasts that are cell cycle arrested by overexpression of the growth arrest specific 1 GAS1 protein^[83]. In agreement, depletion of DYRK1B by RNA interference (RNAi) enables G0-arrested NIH3T3 fibroblasts and C2C12 myoblasts to re-enter the cell cycle, whereas transient overexpression of DYRK1B arrests dividing cells at G0^[70,82,84].

Except in fibroblasts and myoblasts, DYRK1B is highly expressed in testis, where it negatively regulates proliferation of immature male germ cells^[77]. In addition, DYRK1B is strongly up-regulated in solid tumors and carcinoma cell lines, as mentioned above. Depletion or inhibition of DYRK1B promotes cell cycle re-entry of quiescent cancer cells, indicating that DYRK1B is sufficient to maintain cancer cells in a quiescent state^[80]. DYRK1B promotes the maintenance of G0 arrest of differentiating non-transformed myoblasts, NIH3T3 fibroblasts and Mv1Lu epithelial cells by post-translational mechanisms^[24]. The regulation of cell cycle by DYRK1B is achieved by the phosphorylation of cell cycle regulators, such as cyclin D isoforms and p27^{Kip1}, leading to their degradation and stability, respectively. Especially, DYRK1B binds to GSK3 β , and this kinase complex phosphorylates cyclin D1 at two adjacent conserved ubiquitination sites as follows: DYRK1B at Thr288 and GSK3 β at Thr286, respectively, destabilizing and leading cyclin D1 to proteasomal degradation in the cytoplasm^[35,84].

Also, DYRK1B stabilizes the cyclin-dependent kinase (CDK) inhibitor p27^{Kip1} by phosphorylation at Ser10. Phosphorylation of p27^{Kip1} prevents its cytoplasmic translocation and its subsequent proteasomal degradation^[23,82,84,85].

The implication of DYRK1B and DYRK1A in the regulation of cell cycle occurs *via* an additional mechanism involving the DREAM complex which consists of MuvB, RB2, E2F4 and DP proteins. Both kinases activate the DREAM complex by phosphorylating LIN52, a subunit of MuvB at the Ser28 residue^[86]. The DREAM complex is a major coordinator of the cell cycle and is essential to maintain the quiescent state^[87]. LIN52 may be involved in long-term regulation of cell fate^[80,88] (Figure 2).

Prosurvival function of DYRK1B in myogenesis and cancer

In a large-scale RNAi screen using HeLa carcinoma cells, DYRK1B and DYRK3 have been identified as prosurvival kinases^[59]. In another study, Mercer and colleagues^[69] demonstrated that DYRK1B blocks apoptosis through phosphorylation of p21^{Cip1}, which occurs during the differentiation of C2C12 myoblasts. DYRK1B diminishes the extent of myoblast apoptosis through phosphorylation of p21^{Cip1} at the nuclear localization domain, resulting in its cytoplasmic relocation and rendering p21^{Cip1} unable to mediate cell cycle arrest^[68,69]. The DYRK1B-induced change in p21^{Cip1} intracellular localization accompanies myoblast differentiation. Endogenous p21^{Cip1} is localized exclusively to the nuclei of proliferating myoblasts, whereas it is relocated at the cytoplasm of post-mitotic multinucleated myotubes and adult human skeletal myofibers. The p21^{Cip1} cytoplasmic portion forms a physical complex with the apoptosis signal-regulating kinase 1 (known as ASK1), an upstream activator of the caspase cascade, which blocks apoptosis through the inhibition of caspase 3^[67,69]. In agreement, knockdown experiments of endogenous DYRK1B by RNAi in C2C12 myoblasts resulted in decreased myoblast survival by 75%, whereas transient overexpression of DYRK1B increased cell viability^[69].

Moreover, depletion of DYRK1B by RNAi or pharmacological inhibition of DYRK1B kinase activity impairs cell survival and induces apoptosis, in many cancer cell lines^[39,48,53,58,89]. This is concomitant with the increased intracellular levels of reactive oxygen species (ROS) in pancreatic cancer^[49,50,52], ovarian cancer^[41,51,89], colon cancer^[51], and osteosarcoma^[90]. Increased ROS levels that followed DYRK1B depletion are accompanied with DNA damage, as indicated by phosphorylation of histone 2AX (known as H2AX) at Ser139 by ribosomal S6 kinase 2 (known as RSK2)^[91], in pancreatic^[49,50,52] and ovarian^[41,51,80,89] cancers. In addition, DYRK1B up-regulates expression of several antioxidant genes, *e.g.*, ferroxidase and superoxide dismutases 2 and 3 (known as SOD2 and SOD3 respectively) in cancer cell lines^[38,49,51,80]. The increased expression of antioxidant genes may be due to the fact that cancer cells maintain higher ROS levels than normal cells and might, thus, be more sensitive to further accumulation of ROS^[80,92]. It has been proposed that targeting of the antioxidant mechanisms of cancer cells and the subsequent increase in intracellular cellular ROS levels may be a potential strategy for anticancer therapies^[93]. Thus, depletion or pharmacological inhibition of DYRK1B will sensitize cancer cells to chemotherapeutic drugs, such as cisplatin, that increase ROS levels^[38,45].

A third mechanism concerning the role of DYRK1B in cell survival, except p21^{Cip1} intracellular distribution and regulation of ROS levels, includes the nuclear exclusion and subsequent inactivation of NKX3.1 and the forkhead box O (FOXO) transcription factors, FOXO1 and FOXO3A^[72,80,94], mediated by DYRK1B phosphorylation. NKX3.1 and FOXO factors act as tumor suppressors in several cancers by suppressing cell proliferation and promoting apoptosis^[95]. DYRK1B abolishment was shown to enhance nuclear translocation of FOXO1 and FOXO3A and increase apoptosis in ovarian cancer cells^[72,80] (Figure 2).

DYRK1B maintains quiescence in CSCs

In cancer tumors, there is a subpopulation of cells that possess stemness features. These CSCs, also known as the tumor-initiating cells, are cells capable of maintaining themselves *via* self-renewal and restoration^[96]. CSCs are responsible for tumor growth and metastasis, making them a prime target for efficient therapeutic interventions. However, CSCs are extremely resistant to current therapeutic approaches, implicating them as the main reason for cancer recurrence^[97]. Stem cells from various cancers have been reported to be often quiescent^[98]. The relative resistance of CSCs to chemo- and radio-therapies, both targeting dividing cells, is due to the ability of some CSCs to remain in a non-dividing quiescent state (G0)^[42,97,99]. A portion of pancreatic cancer cells out of the cell cycle may be post-mitotic, while other pancreatic cancer cells out of cell cycle seem to be in a quiescent, reversible G0 state, thus remaining resistant to drugs

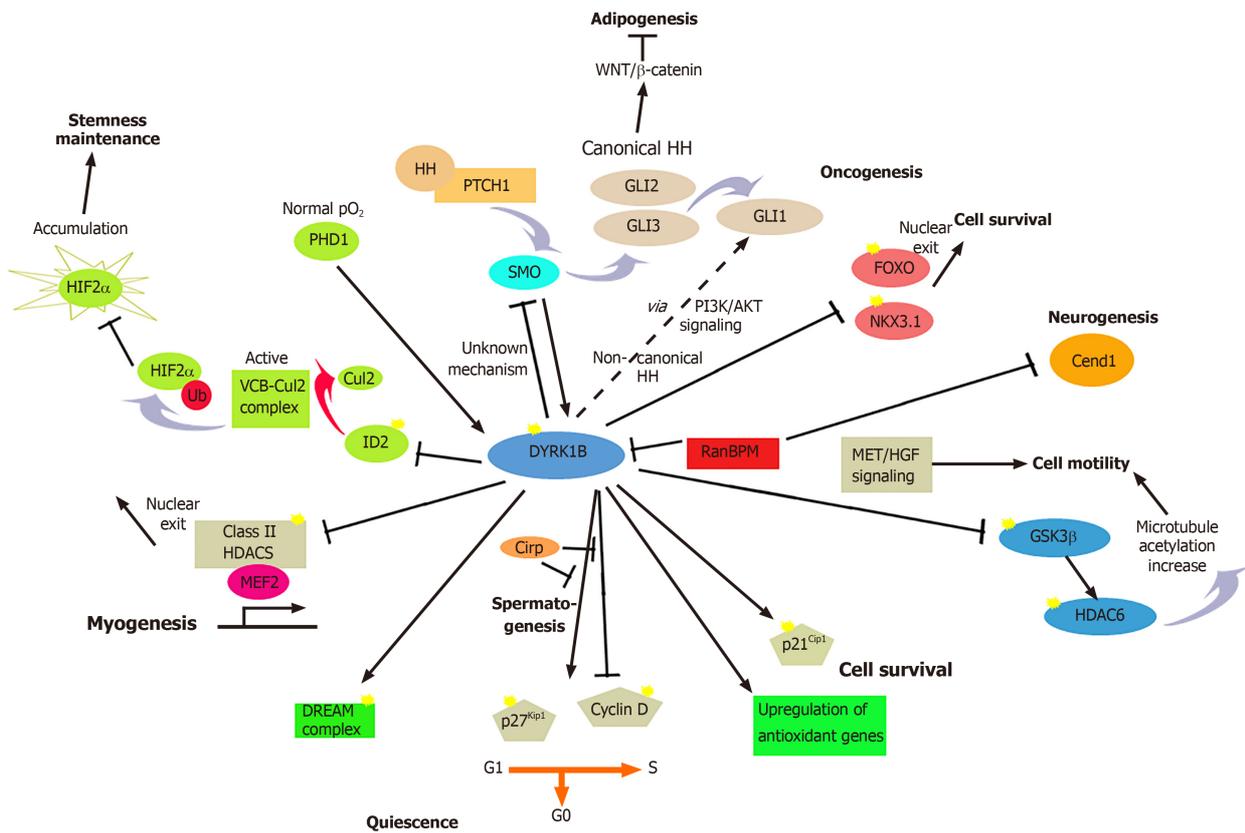


Figure 2 Summary of the major known functions of dual-specificity tyrosine-regulated kinase 1B in development and disease. Dual-specificity tyrosine-regulated kinase 1B (DYRK1B) plays a critical role in many biological processes in development and human diseases, regulating cell cycle progression/exit, differentiation, transcription, and cell survival and motility. DYRK1B facilitates growth arrest and promotes quiescence (G0) by stabilizing cyclin-dependent kinase inhibitor p27^{Kip1} and destabilizing cyclin D1, via phosphorylation. The anti-proliferative function of DYRK1B occurs in myogenesis, spermatogenesis, neurogenesis, and cancer. Moreover, DYRK1B maintains quiescence by stabilization of the DREAM complex via phosphorylation of LIN52, a subunit of MuvB in the complex. In oncogenesis, DYRK1B induces degradation of the tumor suppressor NKX3.1, while reducing the activity of tumor suppressors and apoptotic promoters of the forkhead box O (FOXO) family, resulting in survival of cancer cells and enhancement of oncogenic GLI1 activity. The prosurvival function of DYRK1B in myogenesis and cancer is mediated through phosphorylation of p21^{Cip1}, DYRK1B counteracts oxidative stress by reducing intracellular levels of oxygen reactive species (ROS) through the up-regulation of antioxidant genes. DYRK1B modulates stemness of cancer stem cells. In normoxia, oxygen-sensing prolyl-hydroxylase (PHD1) activates DYRK1B, which inactivates ID2, makes it unable to displace the Cul2 component from the VCB-Cul2 ubiquitin ligase complex, which remains active, promoting HIF2α degradation. In hypoxia, PHD1 and DYRK1B are inactivated, leading to activated ID2 and resulting in HIF2α accumulation that facilitates cancer stem cell maintenance. DYRK1B is involved in a complex cross-talk with hedgehog (HH). DYRK1B inhibits canonical HH signaling initiated by Smoothed (SMO), while it promotes non-canonical HH signaling by promoting PI3K-AKT-mediated stability of the GLI1 transcription factor. In metabolic syndrome, DYRK1B inhibits sonic hedgehog (SHH) and Wnt signaling, enhancing adipogenesis. In spermatogenesis, DYRK1B interacts with cold-inducible RNA-binding protein (Cirp), resulting in destabilization of p27^{Kip1} and cyclin D1 stabilization that promote cell cycle progression of undifferentiated spermatogonia. In myogenesis, DYRK1B inactivates Class II histone deacetylases (HDACs), resulting in myogenic regulatory factor (MEF) 2-dependent transcription of myogenic genes. In neurogenesis, tripartite functional interactions between DYRK1B, RanBPM and the neuronal protein Cend1 regulate the balance between cellular proliferation and differentiation. Increased levels of DYRK1B block cell motility through interaction with the adaptor protein RanBPM and Met/HGF signaling. DYRK1B modifies indirectly the microtubules, through phosphorylation of GSK3β and subsequent inactivation of HDAC6, leading to increase of microtubules acetylation. Dashed lines represent indirect mechanisms and yellow stars represent phosphorylations. ERK: Extracellular signal-regulated kinases.

and able to repopulate the tumor^[11]. DYRK1B kinase could be of clinical relevance, since it is included among the factors which allow the survival of quiescent CSCs *in vivo*^[98]. As we have mentioned above, DYRK1B is highly expressed in several cancers and it was found to be amplified or hyperactive in ovarian and pancreatic cancers^[18,37,40]. Experimental data suggest that increased levels of DYRK1B are related to tumor development and poor outcome^[43]. Also, it is known that the orthologous DYRK1A kinase is implicated in cancer, with a partially similar role as that of DYRK1B^[100-109]. DYRK1B has been shown to confer on CSCs the ability to remain in a quiescent state, in such a way that when exposed to therapeutic agents/drugs (chemotherapy) or radiation (radiotherapy), making them chemo- and radio-resistant by controlling the balance between quiescence and apoptosis^[36,53,56,106,110]. Thus, the wake-up of quiescent CSCs may be achieved using DYRK1B pharmacological inhibitors, which could serve as potent drugs in cancer therapy^[43,80]. Moreover, DYRK1B may be used as a diagnostic marker and survival factor for various types of human cancer^[43].

DYRK1B regulates the maintenance of CSCs under hypoxia or normoxia

The stemness capacity of stem cells depends on the balance of complex signals in their microenvironment^[111]. It has been suggested^[111,112] that stem cells are localized in a microenvironment of low oxygen, indicating that hypoxia may be a critical factor for stem cell maintenance and that low oxygen tension in cell culture has positive effects on the survival and self-renewal of stem cells. Furthermore, a hypoxic microenvironment assists in maintaining the multipotency of ESCs^[113], the undifferentiated state of hematopoietic, mesenchymal and NSCs, and in the regulation of proliferation and cell-fate commitment^[111].

Recent advances in cancer research have indicated that mechanisms maintaining CSCs are crucial to tumor progression^[112]. Hypoxia is the most critical factor for the maintenance of stemness, as well as the enhanced expression/activation of hypoxia-inducible factors (HIFs), which frequently occurs in cancer cells during cancer progression. The enhanced expression and activation of HIFs is associated with the acquisition of cancer cells with a more malignant behavior, treatment resistance and poor outcome for cancer patients. HIF1 α and HIF2 α are transcription factors that act as key mediators of the adaptation of CSCs to oxygen and nutrient deprivation, during cancer progression, under normoxic and hypoxic conditions^[81]. Especially, the HIF2 α transcription factor is required for maintenance of CSCs.

Another protein that participates and promotes the cancer hallmarks, including CSC state, is the ID2 protein. However, the pathways that are engaged by ID2 or drive HIF2 α accumulation in CSCs still remain unclear^[81]. DYRK1B modulates stemness of CSCs through a mechanism taking place under normoxia or hypoxia conditions. In normoxia, oxygen-sensing prolyl-hydroxylase (PHD1) activates DYRK1B, which inactivates the ID2 protein by phosphorylation at Thr27^[81], making it unable to displace the VHL-associated protein cullin-2 (Cul2) component from the VCB-Cul2 ubiquitin ligase complex, which remains active and capable of promoting HIF2 α degradation^[81] (Figure 2). In contrast, in hypoxia conditions, PHD1 and DYRK1B are inactivated, leading to activated ID2^[81]. Then, the activated ID2 binds to the VHL ubiquitin ligase complex, displacing the Cul2 and subsequently impairing HIF2 α ubiquitination and degradation. Thus, HIF2 α stabilization facilitates CSC maintenance and increases the aggressiveness of human hypoxic brain tumors^[81]. In glioblastoma cell lines, under hypoxia conditions, ID2 positively modulates HIF2 α activity and, conversely, in normoxia conditions, the elevated expression of DYRK1A/1B phosphorylates ID2, promoting HIF2 α destabilization, inhibition of tumor growth, loss of glioma stemness and a more favorable prognosis for patients with glioblastoma^[81] (Figure 2).

MOLECULAR MECHANISMS OF DYRK1B FUNCTION IN DEVELOPMENT AND HUMAN DISEASES

As we have discussed above, DYRKs comprise a family of kinases which are key regulators of signal transduction, cell proliferation, survival, and differentiation^[18]. In particular, DYRK1B is a multifunctional dual-specificity kinase involved in cell cycle progression, differentiation and cell viability^[42,69,70], and plays key roles in a variety of physiological developmental processes during myogenesis^[69,70,74], spermatogenesis^[77], neurogenesis^[35] and cell motility^[55], as well as in as in human diseases, such as cancer^[24,36,39,41,50] and metabolic syndrome^[76].

Identification of molecular mechanisms that regulate signaling pathways, through which DYRK1B exerts aspects of its function, in a positive or negative manner, in development and human diseases, is therefore of great interest. Many studies have identified a close regulatory link between DYRK1B and the hedgehog (HH)/GLI signaling pathway, which is essential during development, stem cell maintenance and cell differentiation, and also plays a crucial role in development of many malignancies^[114-121]. Below, we will discuss in detail the functional integration and cross-talk between DYRK1B and the HH/GLI with other signaling pathways, such as RAS and PI3K/mTOR/AKT, and how this might affect cellular and molecular processes in development, physiology and pathology, focusing on the homeostasis of stem and CSCs, respectively.

DYRK1B implication in HH/GLI signaling in cancer

Elucidation of molecular mechanisms that determine the characteristics of malignancies of CSCs is of great importance. An essential signaling pathway during

mammalian embryonic development, involved in proper tissue patterning, stem cell maintenance and cell differentiation, is the HH/GLI signaling pathway, which also plays a crucial role in tumorigenesis, in development of many pediatric and adult malignancies, such as those of pancreas, lung, prostate, brain, and skin^[114-121]. The 'canonical' HH signaling cascade is initiated in the target cell by the HH ligand binding to the Patched receptor (PTCH1, 2), which is located at the primary cilium, functioning as an antenna-like cell compartment and relieving the repression of Smoothed (SMO) transmembrane protein, a member of the G protein-coupled receptor superfamily. Subsequently, SMO enters the primary cilium and initiates signaling by activating the zinc finger transcription factors, GLI2/3, which are released from Suppressor of Fused (SUFU), in order to translocate into the nucleus and initiate the transcription of HH/GLI target genes, including the *GLI1* oncogene. In the absence of HH ligand, the PTCH represses HH signaling by preventing SMO translocation to the primary cilium, resulting in the inactivation of the GLI effectors^[122-128] (Figure 2).

Transcriptional feedback loops take place in HH signaling in order to fine-tune the entire system. Additional modulation of HH signaling is achieved by several kinases, such as PKA, PKC, GRK2, MEK, ERK, AKT, S6K, and GSK3 β ^[129-138]. Cancer cells often take advantage of these mechanisms in non-canonical modes of signaling, such as HH ligand/receptor-independent activation of GLI transcription factors^[18,118,135,139,140]. The mammalian DYRK1A, DYRK1B and DYRK2 participate in the regulation of HH signaling. Notably, DYRK1A possesses an activating function on GLI1, promoting GLI1 nuclear translocation^[141,142] *via* its direct phosphorylation at Ser102/104/130/132 residues located at NLS^[143] and at Ser408^[144]. Moreover, DYRK1A exerts a negative function by inducing GLI1 degradation through an indirect mechanism that engages the actin cytoskeleton and its regulators^[145]. The dual role of DYRK1A in the regulation of HH signaling is probably due to its interactions with different sets of protein partners that have opposing effects^[138]. On the other hand, DYRK2 has been shown to negatively affect the HH pathway by directly phosphorylating GLI2 at two conserved serine residues, Ser385 and Ser1011, inducing its proteasomal decay^[138,145].

DYRK1B inhibits canonical HH signaling / cross-talk between RAS and HH signaling: DYRK1B has a complicated role in modulation of the HH pathway. A cell-autonomous synergism between RAS and GLI oncogenes during tumor formation in the pancreas, lung and colon carcinomas has been reported^[114-116,118]. DYRK1B can inhibit HH signaling by blocking GLI2, which mainly functions as an activator, and by promoting GLI3R formation, which mainly functions as a repressor^[119]. Specifically, Lauth and colleagues^[119], studying the cross-talk between RAS and HH signaling, found that oncogenic mutant RAS (KRAS) acts as: (1) an inducer of sonic hedgehog (SHH) expression; (2) a potent inhibitor of the canonical (HH-PTCH-SMO-initiated) HH pathway; and (3) a regulator of the non-canonical (TGF β -initiated) HH pathway *via* activation of DYRK1B. Consequently, mutant KRAS induces signaling to neighboring cells (paracrine effect), while at the same time inhibits HH signaling into the cells (autocrine effect), thereby initiating the non-canonical HH pathway by increasing DYRK1B expression through an unknown mechanism. Increased DYRK1B blocks the SMO-induced cascade but is ineffective in cells lacking SUFU, mimicking the effect of mutated KRAS (Figure 2). Lauth *et al.*^[119] suggest that mutant KRAS blocks signaling upstream of SUFU through DYRK1B or that the SMO inhibition is actually SUFU-dependent. Moreover, DYRK1B is not as effective as KRAS in the inhibition of HH signaling, suggesting that RAS also activates inhibitory unknown effectors in addition to DYRK1B.

The inhibitory mechanisms initiated by KRAS may be complex, as several RAS effectors, such as RAF/MEK/ERK, PI3K/AKT and RLF/RAL, are required for full inhibition (Figure 1). Remarkably, DYRK1B kinase can be activated by several RAS effectors, such as Tiam/Rac1, MEK, PI3 kinase and possibly RAL-A^[37,119]. The biological significance of the RAS-mediated HH inhibition in cancer cells, with the participation of DYRK1B, could explain why high GLI1 levels are detrimental to normal but not to CSCs in the brain^[119,146]. Blocking autocrine in favor of paracrine HH signaling may enhance the survival of early CSCs. In addition, the presence of RAS-DYRK1B-HH regulatory network has an important impact in developmental disorders caused by aberrant RAS signaling, such as Noonan, cardio-facio-cutaneous and Costello syndromes^[147]. To summarize, the mutant RAS (*i.e.* KRAS) is a cell-autonomous negative regulator of the HH pathway, participating also in the paracrine HH signaling in lung and pancreatic cancers that have accumulated KRAS mutations. Thus, the mechanism of shift from autocrine towards paracrine signaling mechanisms involving the RAS effector kinase DYRK1B remains to be elucidated^[119].

DYRK1B enhances non-canonical HH signaling: DYRK1B has been shown to increase GLI1 activity, whereas DYRK1B inhibition down-regulates GLI1 expression^[121]. Gruber and colleagues^[121], using pancreatic adenocarcinoma (PANC-1) and Ewing sarcoma cell lines, identified DYRK1B as a critical positive regulator of HH/GLI signaling downstream of SMO (Figure 2). In the DAOY human medulloblastoma cells and mouse embryonic fibroblasts (MEFs) deficient in either PTCH or SUFU, the RNAi knockdown of DYRK1B or its pharmacological inhibition (*e.g.*, with harmine or DYRKi), resulted in remarkable repression of HH signaling and GLI1 expression. Notably, DYRKi inhibitor impairs SMO-dependent and SMO-independent oncogenic GLI activity. These results support the usage of DYRK1B inhibitors for the treatment of HH/GLI-associated cancers, instead of SMO inhibitors which have failed to be efficient for cancer therapy^[121]. Furthermore, the addition of the proteasome inhibitor bortezomib reversed the negative effect of DYRK1B inhibition, suggesting that DYRK1B prevents activated GLI1 and GLI2 forms from proteasomal degradation^[23,121]. The detailed mechanism of GLI1 and GLI2 protein stabilization by DYRK1B remains unclear, and whether stabilization of GLI1 and GLI2 involves direct phosphorylation by DYRK1B or depends on alternative indirect unknown mechanisms, will be further investigated.

DYRK1B regulates HH signaling/cross-talk between PI3K/mTOR/AKT and HH signaling both in positive and negative manners: Interaction of DYRK1B with the mammalian HH/GLI pathway has dual and opposing effects. On one hand, the ectopic expression of DYRK1B in NIH3T3 cells blocks canonical SMO-initiated signaling, *via* an elusive mechanism; on the other hand, overexpressed DYRK1B enhances the protein stability of GLI1, by preventing its proteasomal degradation. Stabilization of GLI1 is most likely executed through the AKT pathway^[137,138], which is activated by DYRK1B. AKT subsequently phosphorylates and protects GLI transcription factors from degradation^[130,137,148] (Figures 1 and 2). The exact mechanism of AKT stimulation by DYRK1B is currently unknown^[137]. In addition, because DYRK1B activates the PI3K/mTOR/AKT pathway, the DYRK1B-HH/GLI pathway is subjected to pronounced feedback control^[137] (Figures 1 and 2). In agreement, stimulation of the HH pathway by SMO activation increases DYRK1B protein levels, by unknown post-transcriptional mechanisms, suggesting the ability of HH signaling to stimulate AKT phosphorylation^[137] (Figure 2). In accordance, pharmacological inhibition of the PI3K/AKT/mTOR pathway, performed in pancreatic cancer cell lines (Panc1, AsPc1, SU86.86, CAPAN2 and BxPc3), resulted in up-regulation of DYRK1B kinase and conversely when AKT signaling was activated the DYRK1B mRNA levels were reduced^[51].

The pharmacological inhibition of DYRK1B results in initial up-regulation of HH, followed by down-regulation of AKT phosphorylation, reducing GLI stabilization due to the fact that the PI3K/AKT/mTOR pathway is itself subjected to strong negative feedback regulation^[137]. It has been shown that short-term inhibition of DYRK1B by siRNA resulted in an enhancement of HH signaling, whereas long-term blockade of DYRK1B function by short-hairpin RNA resulted in suppression of GLI1 levels in Panc1 cells^[137]. Furthermore, the involvement of DYRK1B mutations in metabolic syndrome concerning PI3K signaling is intriguing^[76,149,150], as we will mention below. Summarizing, the crosstalk between DYRK1B and HH signaling has to be further elucidated, since the DYRK1B function related to the HH pathway is dependent on DYRK1B expression levels and canonical/non-canonical HH signaling.

DYRK1B regulates cell motility

DYRK1B kinase exerts its function in the regulation of cell motility *via* two discrete mechanisms: HH-induced microtubule (MT) acetylation and Met/ hepatocyte growth factor (HGF) signaling. DYRK1B, through HH signaling, facilitates MT-dependent processes, such as intracellular mitochondrial transport, mesenchymal cell polarization, and directed cell migration. HH signaling affects MT acetylation in mammalian cells^[151]. Using the NIH3T3, HeLa and MEF cell lines, it has been shown that HH pathway activity increases the levels of the MT-associated acetylation *via* a mechanism in which DYRK1B participates^[151]. GSK3 β is inhibited by its phosphorylation at Ser9 by DYRK1B, resulting in suppression of HDAC6 enzyme activity. The inhibition of HDAC6, that represents a major tubulin deacetylase, subsequently increases the levels of acetylated MTs. In summary, intercellular communication *via* HH signals can regulate the MT cytoskeleton and contribute to MT-dependent processes by altering the level of tubulin acetylation through DYRK1B activation^[151]. This could explain the reason that pancreatic cancer cells overexpressing

DYRK1B have shown resistance to the MT-depolymerizing agent Nocodazole^[48].

Except regulation of HH-induced microtubule acetylation, DYRK1B has also been shown to act as an inhibitor of cell motility through its interactions with the Met/HGF signaling pathway. In Mv1Lu mink lung epithelial cells, DYRK1B overexpression inhibited the migration of cells in wound experiments and their invasion through specific polycarbonate filters^[52]. Furthermore, the ability of DYRK1B to inhibit Mv1Lu cell migration was attenuated when cells were exposed to HGF or to elevated levels of transiently expressed RanBPM. RanBPM inhibited the kinase activity of DYRK1B. In addition, RanBPM and HGF inhibited the function of DYRK1B as a transcriptional co-activator. These findings suggest that DYRK1B plays a role in modulating cell migration through opposing the action of RanBPM, which is a Met signaling cascade adaptor protein. Met plays an important role in tumor cell invasion and cell migration. RanBPM has been reported to bind to the tyrosine kinase domain of the HGF receptor Met, enhance Met downstream signaling, and enhance HGF-induced A704 kidney carcinoma cell invasion, as a study has demonstrated^[53]. Moreover, *DYRK1B* was found to be one of the four most promigratory genes in the highly motile SKOV3 tumor cells by an RNAi screen of > 5200 genes^[54]. It is possible that motility induced by oncogenic KRAS was due to DYRK1B activity^[37]. In contrast, another study has shown that inhibition of DYRK1B suppresses the proliferation and migration of liposarcoma cells, indicating a positive role for DYRK1B in cell motility^[55]. In particular, DYRK1B targeting in liposarcoma cells, with small molecule inhibitor AZ191 or RNAi-mediated knockdown, results in reduction of proliferation, as well as in suppression of cell motility, induction of apoptosis, and sensitization of liposarcoma cells to chemotherapy drugs, indicating that DYRK1B could play a significant role in liposarcoma cell growth and proliferation motility^[55].

DYRK1B in metabolic syndrome

Except cancer, very little is known about the implication of DYRK1B in human diseases. Nevertheless, DYRK1B was found to be implicated in a rare autosomal-dominant form of metabolic syndrome, called abdominal obesity metabolic syndrome (or AOMS3) with its two missense mutations H90P and R102C. Affected individuals develop early-onset central obesity, diabetes, coronary artery disease, and hypertension^[76]. The overexpression of DYRK1B-H90P or DYRK1B-R102C mutations in HepG2 hepatoma cells resulted in increased induction of glucose-6-phosphatase (G6Pase), a gluconeogenic enzyme, in a dose-dependent manner^[76]. In addition, the DYRK1B-R102C mutation enhances the effect of DYRK1B on the adipogenic differentiation of 3T3-L1 preadipocytes^[76], as we will discuss below.

Cell-based assays have shown that the mutant alleles behave as gain-of-function variants of DYRK1B^[76], although the kinase activity of DYRK1B-R102C mutant was found to be reduced in *in vitro* assays, while the kinase activity of DYRK1B-H90P mutation has not yet been studied^[55]. It has been shown that H90P and R102C mutations are located at the N-terminal of DYRK1B catalytic domain^[26] and, thus, are unlikely to be directly involved in substrate recognition and catalysis^[65]. There is evidence that these mutations affect the DH box, not directly by interfering with the conformation of the catalytic domain, but by interfering with the HSP90 chaperone/CDC379 co-chaperone-mediated maturation of DYRK1B kinase by tyrosine autophosphorylation. This perturbs the conformational thermodynamic stability of the catalytic domain, which renders the kinase susceptible to misfolding and resulting in its intracellular aggregation^[65]. These findings, described above, point to a role for DYRK1B in adipogenesis and glucose homeostasis, providing a link between DYRK1B altered function and an inherited form of the metabolic syndrome. In agreement, the overexpression of DYRK1B homologues, DYRK1A and MNB in mice and *Drosophila*, respectively, leads to an increase in food uptake and body weight, and, conversely, their deficiencies are associated with loss of body weight^[76,156].

DYRK1B signaling in adipogenic transformation and glucose homeostasis: DYRK1B plays a central role in signaling pathways disrupted in metabolic syndrome, which is another example of cross-talk between DYRK1B and HH, which occurs during differentiation of mesenchymal stem cells into adipocytes^[76]. The HH pathway has an inhibitory function on adipocytic differentiation, involving redirecting cellular fate towards the osteogenic lineage^[18,157-159]. In contrast, DYRK1B favors differentiation into adipocytes^[76]. As we mentioned above, DYRK1B inhibits SHH signaling^[119] and its expression is increased dramatically during adipogenic differentiation^[63]. Also, it has been demonstrated that inhibition of the SHH pathway results in decreased expression of Wnt proteins^[160,161], which are negative regulators of adipogenesis^[162].

In a study by Keramati and colleagues^[76], elucidation of the mechanism of metabolic

syndrome was achieved by examining the effects of DYRK1B, DYRK1B-R102C and knockdown of DYRK1B during adipogenic differentiation of 3T3-L1 preadipocyte cells, using an adipogenic medium containing the Wnt inhibitor IBMX. This approach revealed that DYRK1B protein inhibits SHH through the reduction of the GLI2 effector and the subsequent reduction of Wnt signaling, resulting in enhanced adipogenesis^[76] (Figure 2). Moreover, the DYRK1B-R102C mutation exhibits a maximally strong effect, compared to DYRK1B, in the inhibition of SHH pathway *via* GLI2 effector. Additionally, DYRK1B-R102C mutation suppresses Wnt signaling, revealing its gain-of-function properties^[76]. Notably, DYRK1B is a nutrient-sensing protein that inhibits the RAS-RAF-MEK pathway^[42], which is responsible for the regulation of glucose uptake and glycolysis^[163]. It is known that activation of the MEK pathway results in decreased expression of the *G6Pase* gene and lowers glucose output^[164] (Figure 1).

DYRK1B in myogenesis

DYRK1B has strong expression in differentiated skeletal muscle, indicating a physiological role in muscle development and function. DYRK1B is expressed at low levels in most tissues, including dividing myoblasts, while is increased dramatically, at least 10-fold, when myoblasts undergo terminal differentiation and is maintained at elevated levels in mature muscle cells^[18,70]. Overexpression of DYRK1B facilitated myoblasts to fuse more rapidly when placed in differentiation medium. DYRK1B favors myoblast fusion and the subsequent expression of differentiation markers, such as myogenin, troponin T and muscle myosin heavy chain; while, its depletion, by siRNA, prevents myoblast fusion into myotubes and inhibits the induction of differentiation markers^[70].

Moreover, it is known that induction of DYRK1B within the initial 24 h of myogenic differentiation, enables the transcription of myogenin, which is a myogenic regulatory factor (MRF), through indirect activation of another MRF, the MEF2^[74]. More specifically, DYRK1B relieves MEF2 from HDAC5, HDAC7 and MITR (the MEF2-interacting transcriptional repressor), in a dose- and kinase-dependent manner, by phosphorylating the class II HDACs (HDAC5 and HDAC7), at a conserved serine residue located at the nuclear localization sequence, resulting in decreased nuclear accumulation of Class II HDACs and leading them to exit the nucleus^[74] (Figure 2).

The ability of DYRK1B to activate myogenin transcription facilitates myoblast differentiation. In addition, DYRK1B promotes myoblast differentiation by mediating cell cycle arrest of proliferating myoblasts and by increasing their survival during differentiation^[74]. Also, DYRK1B has been shown to increase the survival of rhabdomyosarcoma cells^[18,53,69]. The induction of DYRK1B under stress conditions suggests that DYRK1B could play a role in response to cellular injury. Skeletal muscle regeneration after injury is achieved by the activation of quiescent muscle stem cells (satellite cells), which enter the cell cycle and then differentiate and fuse with uninjured muscle fibers, in order to repair the damage^[165]. DYRK1B is expressed at low levels in muscle stem cells and its expression is increased when quiescent muscle stem cells are activated to re-enter the cell cycle^[70]. DYRK1B seems to be unimportant for muscle embryonic development, because DYRK1B knockout mice were viable for 18 d after conception, a crucial period for the development of skeletal muscle^[63]. Thus, DYRK1B seems to function more during the repair of normal skeletal muscle^[53]. Studies of DYRK1B in differentiating C2C12 myoblasts strongly suggest that DYRK1B functions as a survival factor, particularly during skeletal muscle regeneration^[53].

DYRK1B has anti-apoptotic functions in both differentiating myoblasts and muscle-related cancer cells, as mentioned above. The anti-apoptotic properties of DYRK1B are also observed in skeletal myoblasts, where DYRK1B is most abundant. A large portion (20%-30%) of cycling myoblasts are not able to differentiate and undergo apoptosis when deprived of mitogens. Depletion of DYRK1B by RNAi blocked myoblast survival and increased the activation of caspase-3^[69]. Moreover, overexpression of DYRK1B eliminated apoptosis during muscle differentiation, whereas overexpression of a DYRK1B dominant negative showed no anti-apoptotic activity^[69]. Muscle satellite cells constitute a self-renewing pool of stem cells in adult muscle, where they function in tissue growth and repair. Disruption of regulatory control between proliferation and differentiation of these cells results in tumor formation^[166]. Notably, although the precise cause of rhabdomyosarcoma is unknown, it has been suggested that cancer arises in 'satellite' stem cells^[75]. It is likely that DYRK1B also facilitates the survival of CSCs of rhabdomyosarcoma, thereby rendering DYRK1B as a novel therapeutic target in rhabdomyosarcoma^[53].

DYRK1B signaling in myogenesis: SHH regulates the cell fate of adult muscle satellite cells in mammals, promoting proliferation of satellite cells and of C2C12

myoblasts and preventing their differentiation into multinucleated myotubes^[166]. DYRK1B seems to have the opposite effect compared to SHH signaling, in muscle stem cells (satellite cells) as well as in C2C12 progenitors^[18]. It remains elusive if the influence of SHH or DYRK1B takes place at the same developmental stage. Experimental data suggest a primarily antagonistic relationship between these two pathways^[18]. On one hand, DYRK1B dampens SMO-induced HH signaling but, on the other hand, it promotes stability of the GLI1 effector *via* DYRK1B-induced stimulation of the PI3K-AKT pathway^[119,121,130,137,167] (Figure 2).

In agreement, other members of the DYRK/MNB/HIPK kinases family have been shown to regulate the transition from growth to differentiation, *e.g.*, the related kinase, Yak1, acts as a growth attenuator in response to stresses and nutrient conditions in yeast^[168] and the YakA kinase regulates stress responses in *Dictyostelium discoideum* in response to nutrient starvation^[169]. In this line, DYRK1B induction complements the observations in myoblast differentiation, as response to growth factor deprivation, as previously described.

DYRK1B in spermatogenesis

DYRK1B is also highly expressed, excepting skeletal muscle, in testis where it negatively regulates proliferation of immature male germ cells by an indirect mechanism^[77]. In adult mouse, spermatogenesis is maintained by germ-line stem cells that undergo mitosis and self-renew or differentiate into committed spermatogonia, which called undifferentiated spermatogonia^[170]. Undifferentiated spermatogonia or spermatogonial stem cells (SSCs)^[77,170] constitute less than 1% of total testicular cells and differentiate into differentiating spermatogonia, which will finally undergo meiosis^[171,172].

Cold-inducible RNA-binding protein (Cirp) is a cold-shock protein identified in mammals. It is induced in response only to mild hypothermia and is also induced by cellular stress, such as ultraviolet irradiation and hypoxia^[173-175]. In response to stress, Cirp migrates from the nucleus to the cytoplasm and affects expression of its target mRNAs^[176,177]. Cirp is expressed in the murine germ cells and its expression levels vary depending on the stage of differentiation^[178]. When mouse testis is exposed to heat stress, expression of Cirp is decreased, in response to the heat-induced testicular damage. Cirp-knockout (*cirp*^{-/-}) mice did not show gross abnormality or defect in fertility but did show significantly reduced number of undifferentiated spermatogonia and exhibited delayed recovery of spermatogenesis after treatment with busulfan, a cytotoxic agent^[77]. It was found that Cirp accelerates cell cycle progression from G0 to G1 as well as from G1 to S phase in cultured MEFs. Notably, in undifferentiated spermatogonia, Cirp and DYRK1B co-localized in the nucleus. The interaction between Cirp and DYRK1B is required to fully maintain the undifferentiated spermatogonia in mice, by promoting their proliferation^[77]. In particular, direct binding of Cirp to DYRK1B prevents DYRK1B binding to p27^{Kip1}, resulting in decreased phosphorylation and destabilization of p27^{Kip1} (Figure 2). In contrast, Cirp did not affect DYRK1B binding to cyclin D1 but inhibited phosphorylation of cyclin D1 by DYRK1B, resulting in cyclin D1 stabilization (Figure 2). In the spermatogonial GC-1spg cell line, suppression of Cirp expression resulted in increased levels of p27^{Kip1} and decreased levels of cyclin D1. Consistent changes in the protein levels of p27^{Kip1} and cyclin D1, as well as the percentage of cells in G0 phase, were observed in undifferentiated spermatogonia of *cirp*^{-/-} mice^[77].

Those findings demonstrated a physiological function of the mammalian cold-shock protein Cirp that explains partly why testis should be kept cool. Cirp fine-tunes cell-cycle progression/exit in undifferentiated spermatogonia, fibroblasts, and cancer cells^[179], by suppressing DYRK1B and modulating the protein levels of cell cycle regulators p27^{Kip1} and cyclin D1. Moreover, Cirp suppresses growth signals indirectly through discrete protein-protein and protein-RNA interactions, which depend on multiple factors, including cell types, stress, and conditions of cells^[77].

DYRK1B in neurogenesis

During development of the CNS, coordinated regulation of cell cycle progression/exit and differentiation of NSCs/NPCs is essential for the proper formation and function of the nervous system^[180-183]. During CNS development, NSCs undergo symmetric and asymmetric divisions and finally exit cell cycle and subsequently differentiate to obtain discrete neuronal identities^[182,184,185]. A number of studies have shown that key regulators of cell cycle progression can influence neural cell fate and differentiation program and reverse cell fate determinants and differentiation-inducing factors can regulate cell cycle progression^[186-189].

Many studies have shown that DYRK1A has an important role in neurogenesis. Hyperactivity or increased gene dosage (*e.g.*, in trisomy 21) of DYRK1A has been linked with abnormal brain development, neurodegeneration^[105], cognitive disabilities and early onset Alzheimer's disease in individuals with Down syndrome^[29,32,34,105,190]. Additional studies have shown that DYRK1A mutations, resulting in loss-of-function, are responsible for intellectual disabilities accompanied by microcephaly, epilepsy and autism, which are generally referred to as autosomal dominant mental retardation 7 syndrome (known as MRD7)^[22,33,34,191,192].

Although the role of DYRK1A in neurogenesis is well documented, the function of its closely related kinase, DYRK1B, in CNS development remains elusive. It is difficult to figure out the functional diversity between DYRK1A and DYRK1B, since the two molecules have been studied in discrete systems. Most of the studies of DYRK1A have been performed in models of neurogenesis, whereas most of the studies of DYRK1B have been performed in models of myogenesis^[69,70,74] and cancers^[24,36,39,41,50].

We have recently demonstrated that DYRK1B is expressed in the adult mouse brain and in cultured primary cortical neurons and we have first studied DYRK1B function in mouse neuroblastoma Neuro2A cells, a suitable model for studies of neuronal development. We found that DYRK1B overexpression in Neuro2A cells promotes cell cycle exit and neuronal differentiation, by promoting Cyclin D1 cytoplasmic relocation and its proteasomal degradation by 26S proteasome^[35,79]. It is worthy of note that transient overexpression of DYRK1B in Neuro2A cells also promotes neuronal differentiation, as indicated by the increase of the mean neurite length by 2-fold and by the expression of the neuronal marker, β III-tubulin, when Neuro2A cells were subjected to differentiation using retinoic acid^[35]. Further, in Neuro2A cells, DYRK1B-dependent down-regulation of Cyclin D1 was reversed following DYRK1B interaction with the scaffolding protein RanBPM. Interestingly, binding of RanBPM to DYRK1B stabilized Cyclin D1 in the nucleus and increased 5-bromo-2'-deoxyuridine (commonly known as BrdU) incorporation, which was used as a measure of cellular proliferation. Moreover, we have found that RanBPM facilitated DYRK1B proteasomal turnover^[35].

In addition, we have demonstrated that the tripartite functional interactions between DYRK1B, RanBPM and the neuronal protein Cend1 (termed for cell cycle exit and neuronal differentiation 1; also known as BM88) regulate the balance between cellular proliferation and differentiation in Neuro2A cells, suggesting that the three proteins may also play a similar role in cell cycle progression/exit and differentiation of NSCs/NPCs during neurogenesis^[35,79] (Figure 2). This is in agreement with the fact that both RanBPM and DYRK1B are expressed in neuronal precursors in parallel with Cend1^[35,79]. Recently, we have found that DYRK1B is expressed in embryonic chick and mouse brain and spinal cord, and is highly expressed by cycling NSCs, while DYRK1B expression marks all along the neuronal lineage, suggesting thus DYRK1B implication in proliferation and differentiation of NSCs (Kokkorakis *et al.*, 2020 unpublished data).

CONCLUSION

Stem cells exist in most tissues of the body at all stages of development, from early stages of embryogenesis all the way throughout adult life, with significant roles in patterning during embryogenesis and differentiation of all body tissues. In the adult life, mesenchymal stem cells have roles as repository cells that have the capacity to enable healing, growth and replacement of cells that are lost due to aging or trauma^[6]. CSCs are the mutated equivalents of normal stem cells that share similar characteristics with them, especially the capacity to give rise to all cell types that reside in a particular cancer. CSCs are thus tumorigenic, in contrast to other non-tumorigenic cancer cells. CSCs may generate tumors through the stem cell capacity of self-renewal and differentiation into multiple cell types. CSCs persist in tumors as a distinct population and cause recurrence and metastasis by giving rise to new tumors^[16].

Multiple factors that regulate the physical environments within stem cell niches can significantly influence cell fate decisions. Among these factors, DYRK kinases comprise a family of protein kinases that are highly evolutionarily conserved, from yeast to humans. DYRK kinases are emerging modulators of signal transduction, cell proliferation, survival, and differentiation^[18] and act as inducers of cell cycle exit and quiescence, as well as promote cell viability through their anti-apoptotic functions^[42]. The studies described herein have revealed that DYRK1B kinase is a multifunctional protein implicating several signaling pathways in development and in human diseases, regulating cell functions, such as cell proliferation, differentiation, cell

viability, motility and transcription. The mechanism under which DYRK1B exerts its function each time seems to be cell type- and context-dependent. DYRK1B is involved in cancer, metabolic syndrome, glucose homeostasis, survival, myogenesis, spermatogenesis, adipogenesis and neurogenesis, as we have recently shown^[55] (Kokkorakis *et al.*, 2020 unpublished data). Several of the studies described above have shown that DYRK1B is involved in various signaling pathways, such as HH, RAS and PI3K/mTOR/AKT, while HH comprises the major signaling pathway in which DYRK1B participates. DYRK1B seems to be not required for HH signaling, but it seems to act as a modulator involved in many HH-driven cascades during embryonic development.

DYRK1B has an important role in stem cell biology as is essential for the regulation of the balance between proliferation and differentiation of stem cells during myogenesis, spermatogenesis, and neurogenesis. In human cancers, DYRK1B is crucial for maintaining CSCs in a quiescence state, rendering them resistant to cancer chemo- and radio-therapies by controlling the balance between quiescence and apoptosis. Moreover, DYRK1B regulates the maintenance of CSCs under hypoxia by phosphorylation of the ID2 protein, resulting in the maintenance of stemness. Re-entering of quiescent CSCs into cell cycle may be achieved using DYRK1B pharmacological inhibitors, which may serve as valuable drugs in cancer therapy^[43,80]. Moreover, DYRK1B may be used as a diagnostic marker for various types of human cancer^[43].

ACKNOWLEDGEMENTS

The authors thank Matsas R for discussions and comments.

REFERENCES

- 1 **Weissman IL.** Stem cells: units of development, units of regeneration, and units in evolution. *Cell* 2000; **100**: 157-168 [PMID: 10647940 DOI: 10.1016/S0092-8674(00)81692-X]
- 2 **Wu J, Izpisua Belmonte JC.** Stem Cells: A Renaissance in Human Biology Research. *Cell* 2016; **165**: 1572-1585 [PMID: 27315475 DOI: 10.1016/j.cell.2016.05.043]
- 3 **Chen J, Liu H, Liu J, Qi J, Wei B, Yang J, Liang H, Chen Y, Chen J, Wu Y, Guo L, Zhu J, Zhao X, Peng T, Zhang Y, Chen S, Li X, Li D, Wang T, Pei D.** H3K9 methylation is a barrier during somatic cell reprogramming into iPSCs. *Nat Genet* 2013; **45**: 34-42 [PMID: 23202127 DOI: 10.1038/ng.2491]
- 4 **Miles DC, de Vries NA, Gisler S, Liefink C, Akhtar W, Gogola E, Pawlitzky I, Hulsman D, Tanger E, Koppens M, Beijersbergen RL, van Lohuizen M.** TRIM28 is an Epigenetic Barrier to Induced Pluripotent Stem Cell Reprogramming. *Stem Cells* 2017; **35**: 147-157 [PMID: 27350605 DOI: 10.1002/stem.2453]
- 5 **Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S.** Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* 2007; **131**: 861-872 [PMID: 18035408 DOI: 10.1016/j.cell.2007.11.019]
- 6 **Daniel MG, Pereira CF, Lemischka IR, Moore KA.** Making a Hematopoietic Stem Cell. *Trends Cell Biol* 2016; **26**: 202-214 [PMID: 26526106 DOI: 10.1016/j.tcb.2015.10.002]
- 7 **Wahlster L, Daley GQ.** Progress towards generation of human haematopoietic stem cells. *Nat Cell Biol* 2016; **18**: 1111-1117 [PMID: 27723718 DOI: 10.1038/ncb3419]
- 8 **Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, Jones JM.** Embryonic stem cell lines derived from human blastocysts. *Science* 1998; **282**: 1145-1147 [PMID: 9804556 DOI: 10.1126/science.282.5391.1145]
- 9 **Nandoe Tewarie RS, Hurtado A, Bartels RH, Grotenhuis A, Oudega M.** Stem cell-based therapies for spinal cord injury. *J Spinal Cord Med* 2009; **32**: 105-114 [PMID: 19569457 DOI: 10.1016/B978-0-444-59544-7.00012-3]
- 10 **Zakrzewski W, Dobrzyński M, Szymonowicz M, Rybak Z.** Stem cells: past, present, and future. *Stem Cell Res Ther* 2019; **10**: 68 [PMID: 30808416 DOI: 10.1186/s13287-019-1165-5]
- 11 **Cheung TH, Rando TA.** Molecular regulation of stem cell quiescence. *Nat Rev Mol Cell Biol* 2013; **14**: 329-340 [PMID: 23698583 DOI: 10.1038/nrm3591]
- 12 **Bonnet D, Dick JE.** Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. *Nat Med* 1997; **3**: 730-737 [PMID: 9212098 DOI: 10.1038/nm0797-730]
- 13 **Kuşoğlu A, Biray Avcı Ç.** Cancer stem cells: A brief review of the current status. *Gene* 2019; **681**: 80-85 [PMID: 30268439 DOI: 10.1016/j.gene.2018.09.052]
- 14 **Ailles LE, Weissman IL.** Cancer stem cells in solid tumors. *Curr Opin Biotechnol* 2007; **18**: 460-466 [PMID: 18023337 DOI: 10.1016/j.copbio.2007.10.007]

- 15 **Aponte PM**, Caicedo A. Stemness in Cancer: Stem Cells, Cancer Stem Cells, and Their Microenvironment. *Stem Cells Int* 2017; **2017**: 5619472 [PMID: [28473858](#) DOI: [10.1155/2017/5619472](#)]
- 16 **Gulaia V**, Kumeiko V, Shved N, Cicinskas E, Rybtsov S, Ruzov A, Kagansky A. Molecular Mechanisms Governing the Stem Cell's Fate in Brain Cancer: Factors of Stemness and Quiescence. *Front Cell Neurosci* 2018; **12**: 388 [PMID: [30510501](#) DOI: [10.3389/fncel.2018.00388](#)]
- 17 **Clevers H**. The cancer stem cell: premises, promises and challenges. *Nat Med* 2011; **17**: 313-319 [PMID: [21386835](#) DOI: [10.1038/nm.2304](#)]
- 18 **Singh R**, Lauth M. Emerging Roles of DYRK Kinases in Embryogenesis and Hedgehog Pathway Control. *J Dev Biol* 2017; **5** [PMID: [29615569](#) DOI: [10.3390/jdb5040013](#)]
- 19 **Hanks SK**, Hunter T. Protein kinases 6. The eukaryotic protein kinase superfamily: kinase (catalytic) domain structure and classification. *FASEB J* 1995; **9**: 576-596 [PMID: [7768349](#) DOI: [10.1096/fasebj.9.8.7768349](#)]
- 20 **Manning G**, Whyte DB, Martinez R, Hunter T, Sudarsanam S. The protein kinase complement of the human genome. *Science* 2002; **298**: 1912-1934 [PMID: [12471243](#) DOI: [10.1126/science.1075762](#)]
- 21 **Aranda S**, Laguna A, de la Luna S. DYRK family of protein kinases: evolutionary relationships, biochemical properties, and functional roles. *FASEB J* 2011; **25**: 449-462 [PMID: [21048044](#) DOI: [10.1096/fj.10-165837](#)]
- 22 **Soppa U**, Becker W. DYRK protein kinases. *Curr Biol* 2015; **25**: R488-R489 [PMID: [26079075](#) DOI: [10.1016/j.cub.2015.02.067](#)]
- 23 **Becker W**. Emerging role of DYRK family protein kinases as regulators of protein stability in cell cycle control. *Cell Cycle* 2012; **11**: 3389-3394 [PMID: [22918246](#) DOI: [10.4161/cc.21404](#)]
- 24 **Mercer SE**, Friedman E. Mirk/Dyrk1B: a multifunctional dual-specificity kinase involved in growth arrest, differentiation, and cell survival. *Cell Biochem Biophys* 2006; **45**: 303-315 [PMID: [16845176](#) DOI: [10.1385/CBB:45:3:303](#)]
- 25 **Tejedor F**, Zhu XR, Kaltenbach E, Ackermann A, Baumann A, Canal I, Heisenberg M, Fischbach KF, Pongs O. minibrain: a new protein kinase family involved in postembryonic neurogenesis in Drosophila. *Neuron* 1995; **14**: 287-301 [PMID: [7857639](#) DOI: [10.1016/0896-6273\(95\)90286-4](#)]
- 26 **Becker W**, Joost HG. Structural and functional characteristics of Dyrk, a novel subfamily of protein kinases with dual specificity. *Prog Nucleic Acid Res Mol Biol* 1999; **62**: 1-17 [PMID: [9932450](#) DOI: [10.1016/s0079-6603\(08\)60503-6](#)]
- 27 **Hämmerle B**, Elizalde C, Galceran J, Becker W, Tejedor FJ. The MNB/DYRK1A protein kinase: neurobiological functions and Down syndrome implications. *J Neural Transm Suppl* 2003; 129-137 [PMID: [15068245](#) DOI: [10.1007/978-3-7091-6721-2_11](#)]
- 28 **Martí E**, Altafaj X, Dierssen M, de la Luna S, Fotaki V, Alvarez M, Pérez-Riba M, Ferrer I, Estivill X. Dyrk1A expression pattern supports specific roles of this kinase in the adult central nervous system. *Brain Res* 2003; **964**: 250-263 [PMID: [12576186](#) DOI: [10.1016/S0006-8993\(02\)04069-6](#)]
- 29 **Hämmerle B**, Carnicero A, Elizalde C, Ceron J, Martínez S, Tejedor FJ. Expression patterns and subcellular localization of the Down syndrome candidate protein MNB/DYRK1A suggest a role in late neuronal differentiation. *Eur J Neurosci* 2003; **17**: 2277-2286 [PMID: [12814361](#) DOI: [10.1046/j.1460-9568.2003.02665.x](#)]
- 30 **Wegiel J**, Kuchna I, Nowicki K, Frackowiak J, Dowjat K, Silverman WP, Reisberg B, DeLeon M, Wisniewski T, Adayev T, Chen-Hwang MC, Hwang YW. Cell type- and brain structure-specific patterns of distribution of minibrain kinase in human brain. *Brain Res* 2004; **1010**: 69-80 [PMID: [15126119](#) DOI: [10.1016/j.brainres.2004.03.008](#)]
- 31 **Park J**, Song WJ, Chung KC. Function and regulation of Dyrk1A: towards understanding Down syndrome. *Cell Mol Life Sci* 2009; **66**: 3235-3240 [PMID: [19685005](#) DOI: [10.1007/s00018-009-0123-2](#)]
- 32 **Wegiel J**, Gong CX, Hwang YW. The role of DYRK1A in neurodegenerative diseases. *FEBS J* 2011; **278**: 236-245 [PMID: [21156028](#) DOI: [10.1111/j.1742-4658.2010.07955.x](#)]
- 33 **Soppa U**, Schumacher J, Florencio Ortiz V, Pasqualon T, Tejedor FJ, Becker W. The Down syndrome-related protein kinase DYRK1A phosphorylates p27(Kip1) and Cyclin D1 and induces cell cycle exit and neuronal differentiation. *Cell Cycle* 2014; **13**: 2084-2100 [PMID: [24806449](#) DOI: [10.4161/cc.29104](#)]
- 34 **Arbones ML**, Thomazeau A, Nakano-Kobayashi A, Hagiwara M, Delabar JM. DYRK1A and cognition: A lifelong relationship. *Pharmacol Ther* 2019; **194**: 199-221 [PMID: [30268771](#) DOI: [10.1016/j.pharmthera.2018.09.010](#)]
- 35 **Tsioras K**, Papastefanaki F, Politis PK, Matsas R, Gaitanou M. Functional Interactions between BM88/Cend1, Ran-binding protein M and Dyrk1B kinase affect cyclin D1 Levels and cell cycle progression/exit in mouse neuroblastoma cells. *PLoS One* 2013; **8**: e82172 [PMID: [24312406](#) DOI: [10.1371/journal.pone.0082172](#)]
- 36 **Lee K**, Deng X, Friedman E. Mirk protein kinase is a mitogen-activated protein kinase substrate that mediates survival of colon cancer cells. *Cancer Res* 2000; **60**: 3631-3637 [PMID: [10910078](#)]
- 37 **Jin K**, Park S, Ewton DZ, Friedman E. The survival kinase Mirk/Dyrk1B is a downstream effector of oncogenic K-ras in pancreatic cancer. *Cancer Res* 2007; **67**: 7247-7255 [PMID: [17671193](#) DOI: [10.1158/0008-5472.CAN-06-4099](#)]
- 38 **Hu J**, Nakhla H, Friedman E. Transient arrest in a quiescent state allows ovarian cancer cells to survive suboptimal growth conditions and is mediated by both Mirk/dyrk1b and p130/RB2. *Int J*

- Cancer* 2011; **129**: 307-318 [PMID: 20857490 DOI: 10.1002/ijc.25692]
- 39 **Gao J**, Yang X, Yin P, Hu W, Liao H, Miao Z, Pan C, Li N. The involvement of FoxO in cell survival and chemosensitivity mediated by Mirk/Dyrk1B in ovarian cancer. *Int J Oncol* 2012; **40**: 1203-1209 [PMID: 22159921 DOI: 10.3892/ijo.2011.1293]
- 40 **Davis SJ**, Sheppard KE, Pearson RB, Campbell IG, Gorringer KL, Simpson KJ. Functional analysis of genes in regions commonly amplified in high-grade serous and endometrioid ovarian cancer. *Clin Cancer Res* 2013; **19**: 1411-1421 [PMID: 23362323 DOI: 10.1158/1078-0432.CCR-12-3433]
- 41 **Hu J**, Deng H, Friedman EA. Ovarian cancer cells, not normal cells, are damaged by Mirk/Dyrk1B kinase inhibition. *Int J Cancer* 2013; **132**: 2258-2269 [PMID: 23114871 DOI: 10.1002/ijc.27917]
- 42 **Friedman E**. Mirk/dyrk1B Kinase in Ovarian Cancer. *Int J Mol Sci* 2013; **14**: 5560-5575 [PMID: 23528858 DOI: 10.3390/ijms14035560]
- 43 **Friedman E**. Mirk/Dyrk1B in cancer. *J Cell Biochem* 2007; **102**: 274-279 [PMID: 17583556 DOI: 10.1002/jcb.21451]
- 44 **Jin K**, Ewton DZ, Park S, Hu J, Friedman E. Mirk regulates the exit of colon cancer cells from quiescence. *J Biol Chem* 2009; **284**: 22916-22925 [PMID: 19542220 DOI: 10.1074/jbc.M109.035519]
- 45 **Gao J**, Zheng Z, Rawal B, Schell MJ, Bepler G, Haura EB. Mirk/Dyrk1B, a novel therapeutic target, mediates cell survival in non-small cell lung cancer cells. *Cancer Biol Ther* 2009; **8**: 1671-1679 [PMID: 19633423 DOI: 10.4161/cbt.8.17.9322]
- 46 **Song LN**, Silva J, Koller A, Rosenthal A, Chen EI, Gelmann EP. The Tumor Suppressor NKX3.1 Is Targeted for Degradation by DYRK1B Kinase. *Mol Cancer Res* 2015; **13**: 913-922 [PMID: 25777618 DOI: 10.1158/1541-7786.MCR-14-0680]
- 47 **Bowen C**, Ostrowski MC, Leone G, Gelmann EP. Loss of PTEN Accelerates NKX3.1 Degradation to Promote Prostate Cancer Progression. *Cancer Res* 2019; **79**: 4124-4134 [PMID: 31213464 DOI: 10.1158/0008-5472.CAN-18-4110]
- 48 **Deng X**, Ewton DZ, Li S, Naqvi A, Mercer SE, Landas S, Friedman E. The kinase Mirk/Dyrk1B mediates cell survival in pancreatic ductal adenocarcinoma. *Cancer Res* 2006; **66**: 4149-4158 [PMID: 16618736 DOI: 10.1158/0008-5472.CAN-05-3089]
- 49 **Deng X**, Ewton DZ, Friedman E. Mirk/Dyrk1B maintains the viability of quiescent pancreatic cancer cells by reducing levels of reactive oxygen species. *Cancer Res* 2009; **69**: 3317-3324 [PMID: 19351855 DOI: 10.1158/0008-5472.CAN-08-2903]
- 50 **Ewton DZ**, Hu J, Vilenchik M, Deng X, Luk KC, Polonskaia A, Hoffman AF, Zipf K, Boylan JF, Friedman EA. Inactivation of mirk/dyrk1b kinase targets quiescent pancreatic cancer cells. *Mol Cancer Ther* 2011; **10**: 2104-2114 [PMID: 21878655 DOI: 10.1158/1535-7163.MCT-11-0498]
- 51 **Deng X**, Hu J, Ewton DZ, Friedman E. Mirk/dyrk1B kinase is upregulated following inhibition of mTOR. *Carcinogenesis* 2014; **35**: 1968-1976 [PMID: 24590896 DOI: 10.1093/carcin/bgu058]
- 52 **Deng X**, Friedman E. Mirk kinase inhibition blocks the *in vivo* growth of pancreatic cancer cells. *Genes Cancer* 2014; **5**: 337-347 [PMID: 25352950 DOI: 10.18632/genesandcancer.29]
- 53 **Mercer SE**, Ewton DZ, Shah S, Naqvi A, Friedman E. Mirk/Dyrk1b mediates cell survival in rhabdomyosarcomas. *Cancer Res* 2006; **66**: 5143-5150 [PMID: 16707437 DOI: 10.1158/0008-5472.CAN-05-1539]
- 54 **Yang C**, Ji D, Weinstein EJ, Choy E, Hornicek FJ, Wood KB, Liu X, Mankin H, Duan Z. The kinase Mirk is a potential therapeutic target in osteosarcoma. *Carcinogenesis* 2010; **31**: 552-558 [PMID: 20042639 DOI: 10.1093/carcin/bgp330]
- 55 **Chen H**, Shen J, Choy E, Hornicek FJ, Shan A, Duan Z. Targeting DYRK1B suppresses the proliferation and migration of liposarcoma cells. *Oncotarget* 2018; **9**: 13154-13166 [PMID: 29568347 DOI: 10.18632/oncotarget.22743]
- 56 **Jin K**, Lim S, Mercer SE, Friedman E. The survival kinase Mirk/dyrk1B is activated through Rac1-MKK3 signaling. *J Biol Chem* 2005; **280**: 42097-42105 [PMID: 16257974 DOI: 10.1074/jbc.M507301200]
- 57 **Tang L**, Wang Y, Strom A, Gustafsson JÅ, Guan X. Lapatinib induces p27(Kip1)-dependent G₁ arrest through both transcriptional and post-translational mechanisms. *Cell Cycle* 2013; **12**: 2665-2674 [PMID: 23907131 DOI: 10.4161/cc.25728]
- 58 **Chen Y**, Wang S, He Z, Sun F, Huang Y, Ni Q, Wang H, Wang Y, Cheng C. Dyrk1B overexpression is associated with breast cancer growth and a poor prognosis. *Hum Pathol* 2017; **66**: 48-58 [PMID: 28554575 DOI: 10.1016/j.humpath.2017.02.033]
- 59 **MacKeigan JP**, Murphy LO, Blenis J. Sensitized RNAi screen of human kinases and phosphatases identifies new regulators of apoptosis and chemoresistance. *Nat Cell Biol* 2005; **7**: 591-600 [PMID: 15864305 DOI: 10.1038/ncb1258]
- 60 **Zhou N**, Yuan S, Wang R, Zhang W, Chen JJ. Role of dual specificity tyrosine-phosphorylation-regulated kinase 1B (Dyrk1B) in S-phase entry of HPV E7 expressing cells from quiescence. *Oncotarget* 2015; **6**: 30745-30761 [PMID: 26307683 DOI: 10.18632/oncotarget.5222]
- 61 **Kettle JG**, Ballard P, Bardelle C, Cockerill M, Colclough N, Critchlow SE, Debreczeni J, Fairley G, Fillery S, Graham MA, Goodwin L, Guichard S, Hudson K, Ward RA, Whittaker D. Discovery and optimization of a novel series of Dyrk1B kinase inhibitors to explore a MEK resistance hypothesis. *J Med Chem* 2015; **58**: 2834-2844 [PMID: 25738750 DOI: 10.1021/acs.jmedchem.5b00098]
- 62 **Li Z**, Jiang K, Zhu X, Lin G, Song F, Zhao Y, Piao Y, Liu J, Cheng W, Bi X, Gong P, Song Z, Meng S. Encorafenib (LGX818), a potent BRAF inhibitor, induces senescence accompanied by autophagy in BRAFV600E melanoma cells. *Cancer Lett* 2016; **370**: 332-344 [PMID: 26586345]

- DOI: [10.1016/j.canlet.2015.11.015](https://doi.org/10.1016/j.canlet.2015.11.015)]
- 63 **Leder S**, Czajkowska H, Maenz B, De Graaf K, Barthel A, Joost HG, Becker W. Alternative splicing variants of dual specificity tyrosine phosphorylated and regulated kinase 1B exhibit distinct patterns of expression and functional properties. *Biochem J* 2003; **372**: 881-888 [PMID: [12633499](https://pubmed.ncbi.nlm.nih.gov/12633499/) DOI: [10.1042/BJ20030182](https://doi.org/10.1042/BJ20030182)]
 - 64 **Kinstrie R**, Lochhead PA, Sibbet G, Morrice N, Cleghon V. dDYRK2 and Minibrain interact with the chromatin remodelling factors SNR1 and TRX. *Biochem J* 2006; **398**: 45-54 [PMID: [16671894](https://pubmed.ncbi.nlm.nih.gov/16671894/) DOI: [10.1042/BJ20060159](https://doi.org/10.1042/BJ20060159)]
 - 65 **Abu Jhaisha S**, Widowati EW, Kii I, Sonamoto R, Knapp S, Papadopoulos C, Becker W. DYRK1B mutations associated with metabolic syndrome impair the chaperone-dependent maturation of the kinase domain. *Sci Rep* 2017; **7**: 6420 [PMID: [28743892](https://pubmed.ncbi.nlm.nih.gov/28743892/) DOI: [10.1038/s41598-017-06874-w](https://doi.org/10.1038/s41598-017-06874-w)]
 - 66 **Leder S**, Weber Y, Altafaj X, Estivill X, Joost HG, Becker W. Cloning and characterization of DYRK1B, a novel member of the DYRK family of protein kinases. *Biochem Biophys Res Commun* 1999; **254**: 474-479 [PMID: [9918863](https://pubmed.ncbi.nlm.nih.gov/9918863/) DOI: [10.1006/bbrc.1998.9967](https://doi.org/10.1006/bbrc.1998.9967)]
 - 67 **Asada M**, Yamada T, Ichijo H, Delia D, Miyazono K, Fukumuro K, Mizutani S. Apoptosis inhibitory activity of cytoplasmic p21(Cip1/WAF1) in monocytic differentiation. *EMBO J* 1999; **18**: 1223-1234 [PMID: [10064589](https://pubmed.ncbi.nlm.nih.gov/10064589/) DOI: [10.1093/emboj/18.5.1223](https://doi.org/10.1093/emboj/18.5.1223)]
 - 68 **Zhou BP**, Liao Y, Xia W, Spohn B, Lee MH, Hung MC. Cytoplasmic localization of p21Cip1/WAF1 by Akt-induced phosphorylation in HER-2/neu-overexpressing cells. *Nat Cell Biol* 2001; **3**: 245-252 [PMID: [11231573](https://pubmed.ncbi.nlm.nih.gov/11231573/) DOI: [10.1038/35060032](https://doi.org/10.1038/35060032)]
 - 69 **Mercer SE**, Ewton DZ, Deng X, Lim S, Mazur TR, Friedman E. Mirk/Dyrk1B mediates survival during the differentiation of C2C12 myoblasts. *J Biol Chem* 2005; **280**: 25788-25801 [PMID: [15851482](https://pubmed.ncbi.nlm.nih.gov/15851482/) DOI: [10.1074/jbc.M413594200](https://doi.org/10.1074/jbc.M413594200)]
 - 70 **Deng X**, Ewton DZ, Pawlikowski B, Maimone M, Friedman E. Mirk/dyrk1B is a Rho-induced kinase active in skeletal muscle differentiation. *J Biol Chem* 2003; **278**: 41347-41354 [PMID: [12902328](https://pubmed.ncbi.nlm.nih.gov/12902328/) DOI: [10.1074/jbc.M306780200](https://doi.org/10.1074/jbc.M306780200)]
 - 71 **Lim S**, Jin K, Friedman E. Mirk protein kinase is activated by MKK3 and functions as a transcriptional activator of HNF1alpha. *J Biol Chem* 2002; **277**: 25040-25046 [PMID: [11980910](https://pubmed.ncbi.nlm.nih.gov/11980910/) DOI: [10.1074/jbc.M203257200](https://doi.org/10.1074/jbc.M203257200)]
 - 72 **Gao J**, Zhao Y, Lv Y, Chen Y, Wei B, Tian J, Yang Z, Kong F, Pang J, Liu J, Shi H. Mirk/Dyrk1B mediates G0/G1 to S phase cell cycle progression and cell survival involving MAPK/ERK signaling in human cancer cells. *Cancer Cell Int* 2013; **13**: 2 [PMID: [23311607](https://pubmed.ncbi.nlm.nih.gov/23311607/) DOI: [10.1186/1475-2867-13-2](https://doi.org/10.1186/1475-2867-13-2)]
 - 73 **Lim S**, Zou Y, Friedman E. The transcriptional activator Mirk/Dyrk1B is sequestered by p38alpha/beta MAP kinase. *J Biol Chem* 2002; **277**: 49438-49445 [PMID: [12384504](https://pubmed.ncbi.nlm.nih.gov/12384504/) DOI: [10.1074/jbc.M206840200](https://doi.org/10.1074/jbc.M206840200)]
 - 74 **Deng X**, Ewton DZ, Mercer SE, Friedman E. Mirk/dyrk1B decreases the nuclear accumulation of class II histone deacetylases during skeletal muscle differentiation. *J Biol Chem* 2005; **280**: 4894-4905 [PMID: [15546868](https://pubmed.ncbi.nlm.nih.gov/15546868/) DOI: [10.1074/jbc.M411894200](https://doi.org/10.1074/jbc.M411894200)]
 - 75 **Merlino G**, Helman LJ. Rhabdomyosarcoma--working out the pathways. *Oncogene* 1999; **18**: 5340-5348 [PMID: [10498887](https://pubmed.ncbi.nlm.nih.gov/10498887/) DOI: [10.1038/sj.onc.1203038](https://doi.org/10.1038/sj.onc.1203038)]
 - 76 **Keramati AR**, Fathzadeh M, Go GW, Singh R, Choi M, Faramarzi S, Mane S, Kasaei M, Sarajzadeh-Fard K, Hwa J, Kidd KK, Babaei Bigi MA, Malekzadeh R, Hosseinian A, Babaei M, Lifton RP, Mani A. A form of the metabolic syndrome associated with mutations in DYRK1B. *N Engl J Med* 2014; **370**: 1909-1919 [PMID: [24827035](https://pubmed.ncbi.nlm.nih.gov/24827035/) DOI: [10.1056/NEJMoa1301824](https://doi.org/10.1056/NEJMoa1301824)]
 - 77 **Masuda T**, Itoh K, Higashitsuji H, Higashitsuji H, Nakazawa N, Sakurai T, Liu Y, Tokuchi H, Fujita T, Zhao Y, Nishiyama H, Tanaka T, Fukumoto M, Ikawa M, Okabe M, Fujita J. Cold-inducible RNA-binding protein (Cirp) interacts with Dyrk1b/Mirk and promotes proliferation of immature male germ cells in mice. *Proc Natl Acad Sci U S A* 2012; **109**: 10885-10890 [PMID: [22711815](https://pubmed.ncbi.nlm.nih.gov/22711815/) DOI: [10.1073/pnas.1121524109](https://doi.org/10.1073/pnas.1121524109)]
 - 78 **Aponte PM**. Spermatogonial stem cells: Current biotechnological advances in reproduction and regenerative medicine. *World J Stem Cells* 2015; **7**: 669-680 [PMID: [26029339](https://pubmed.ncbi.nlm.nih.gov/26029339/) DOI: [10.4252/wjsc.v7.i4.669](https://doi.org/10.4252/wjsc.v7.i4.669)]
 - 79 **Gaitanou M**, Segklia K, Matsas R. Cend1, a Story with Many Tales: From Regulation of Cell Cycle Progression/Exit of Neural Stem Cells to Brain Structure and Function. *Stem Cells Int* 2019; **2019**: 2054783 [PMID: [31191667](https://pubmed.ncbi.nlm.nih.gov/31191667/) DOI: [10.1155/2019/2054783](https://doi.org/10.1155/2019/2054783)]
 - 80 **Becker W**. A wake-up call to quiescent cancer cells - potential use of DYRK1B inhibitors in cancer therapy. *FEBS J* 2018; **285**: 1203-1211 [PMID: [29193696](https://pubmed.ncbi.nlm.nih.gov/29193696/) DOI: [10.1111/febs.14347](https://doi.org/10.1111/febs.14347)]
 - 81 **Lee SB**, Frattini V, Bansal M, Castano AM, Sherman D, Hutchinson K, Bruce JN, Califano A, Liu G, Cardozo T, Iavarone A, Lasorella A. An ID2-dependent mechanism for VHL inactivation in cancer. *Nature* 2016; **529**: 172-177 [PMID: [26735018](https://pubmed.ncbi.nlm.nih.gov/26735018/) DOI: [10.1038/nature16475](https://doi.org/10.1038/nature16475)]
 - 82 **Deng X**, Mercer SE, Shah S, Ewton DZ, Friedman E. The cyclin-dependent kinase inhibitor p27Kip1 is stabilized in G(0) by Mirk/dyrk1B kinase. *J Biol Chem* 2004; **279**: 22498-22504 [PMID: [15010468](https://pubmed.ncbi.nlm.nih.gov/15010468/) DOI: [10.1074/jbc.M400479200](https://doi.org/10.1074/jbc.M400479200)]
 - 83 **Pérez-Sánchez G**, Jiménez A, Quezada-Ramírez MA, Estudillo E, Ayala-Sarmiento AE, Mendoza-Hernández G, Hernández-Soto J, Hernández-Hernández FC, Cázares-Raga FE, Segovia J. Annexin A1, Annexin A2, and Dyrk 1B are upregulated during GAS1-induced cell cycle arrest. *J Cell Physiol* 2018; **233**: 4166-4182 [PMID: [29030970](https://pubmed.ncbi.nlm.nih.gov/29030970/) DOI: [10.1002/jcp.26226](https://doi.org/10.1002/jcp.26226)]
 - 84 **Zou Y**, Ewton DZ, Deng X, Mercer SE, Friedman E. Mirk/dyrk1B kinase destabilizes cyclin D1 by

- phosphorylation at threonine 288. *J Biol Chem* 2004; **279**: 27790-27798 [PMID: 15075324 DOI: 10.1074/jbc.M403042200]
- 85 **Ashford AL**, Oxley D, Kettle J, Hudson K, Guichard S, Cook SJ, Lochhead PA. A novel DYRK1B inhibitor AZ191 demonstrates that DYRK1B acts independently of GSK3 β to phosphorylate cyclin D1 at Thr(286), not Thr(288). *Biochem J* 2014; **457**: 43-56 [PMID: 24134204 DOI: 10.1042/BJ20130461]
- 86 **Litovchick L**, Florens LA, Swanson SK, Washburn MP, DeCaprio JA. DYRK1A protein kinase promotes quiescence and senescence through DREAM complex assembly. *Genes Dev* 2011; **25**: 801-813 [PMID: 21498570 DOI: 10.1101/gad.2034211]
- 87 **Sadasivam S**, DeCaprio JA. The DREAM complex: master coordinator of cell cycle-dependent gene expression. *Nat Rev Cancer* 2013; **13**: 585-595 [PMID: 23842645 DOI: 10.1038/nrc3556]
- 88 **Chen JY**, Lin JR, Tsai FC, Meyer T. Dosage of Dyrk1a shifts cells within a p21-cyclin D1 signaling map to control the decision to enter the cell cycle. *Mol Cell* 2013; **52**: 87-100 [PMID: 24119401 DOI: 10.1016/j.molcel.2013.09.009]
- 89 **Hu J**, Friedman E. Depleting Mirk Kinase Increases Cisplatin Toxicity in Ovarian Cancer Cells. *Genes Cancer* 2010; **1**: 803-811 [PMID: 21113238 DOI: 10.1177/1947601910377644]
- 90 **Schmitt C**, Kail D, Mariano M, Empting M, Weber N, Paul T, Hartmann RW, Engel M. Design and synthesis of a library of lead-like 2,4-bis(heterocyclic) substituted thiophenes as selective Dyrk/Clk inhibitors. *PLoS One* 2014; **9**: e87851 [PMID: 24676346 DOI: 10.1371/journal.pone.0087851]
- 91 **Zhu F**, Zykova TA, Peng C, Zhang J, Cho YY, Zheng D, Yao K, Ma WY, Lau AT, Bode AM, Dong Z. Phosphorylation of H2AX at Ser139 and a new phosphorylation site Ser16 by RSK2 decreases H2AX ubiquitination and inhibits cell transformation. *Cancer Res* 2011; **71**: 393-403 [PMID: 21224359 DOI: 10.1158/0008-5472.CAN-10-2012]
- 92 **Trachootham D**, Alexandre J, Huang P. Targeting cancer cells by ROS-mediated mechanisms: a radical therapeutic approach? *Nat Rev Drug Discov* 2009; **8**: 579-591 [PMID: 19478820 DOI: 10.1038/nrd2803]
- 93 **Gorrini C**, Harris IS, Mak TW. Modulation of oxidative stress as an anticancer strategy. *Nat Rev Drug Discov* 2013; **12**: 931-947 [PMID: 24287781 DOI: 10.1038/nrd4002]
- 94 **Woods YL**, Rena G, Morrice N, Barthel A, Becker W, Guo S, Unterman TG, Cohen P. The kinase DYRK1A phosphorylates the transcription factor FKHR at Ser329 *in vitro*, a novel *in vivo* phosphorylation site. *Biochem J* 2001; **355**: 597-607 [PMID: 11311120 DOI: 10.1042/bj3550597]
- 95 **Fu Z**, Tindall DJ. FOXOs, cancer and regulation of apoptosis. *Oncogene* 2008; **27**: 2312-2319 [PMID: 18391973 DOI: 10.1038/onc.2008.24]
- 96 **Phi LTH**, Sari IN, Yang YG, Lee SH, Jun N, Kim KS, Lee YK, Kwon HY. Cancer Stem Cells (CSCs) in Drug Resistance and their Therapeutic Implications in Cancer Treatment. *Stem Cells Int* 2018; **2018**: 5416923 [PMID: 29681949 DOI: 10.1155/2018/5416923]
- 97 **Atashzar MR**, Baharlou R, Karami J, Abdollahi H, Rezaei R, Pourramezan F, Zoljalali Moghaddam SH. Cancer stem cells: A review from origin to therapeutic implications. *J Cell Physiol* 2020; **235**: 790-803 [PMID: 31286518 DOI: 10.1002/jcp.29044]
- 98 **Friedman E**. The Kinase Mirk/dyrk1B: A Possible Therapeutic Target in Pancreatic Cancer. *Cancers (Basel)* 2010; **2**: 1492-1512 [PMID: 24281169 DOI: 10.3390/cancers2031492]
- 99 **Barnes DJ**, Melo JV. Primitive, quiescent and difficult to kill: the role of non-proliferating stem cells in chronic myeloid leukemia. *Cell Cycle* 2006; **5**: 2862-2866 [PMID: 17172863 DOI: 10.4161/cc.5.24.3573]
- 100 **Chang HS**, Lin CH, Yang CH, Yen MS, Lai CR, Chen YR, Liang YJ, Yu WC. Increased expression of Dyrk1a in HPV16 immortalized keratinocytes enable evasion of apoptosis. *Int J Cancer* 2007; **120**: 2377-2385 [PMID: 17294446 DOI: 10.1002/ijc.22573]
- 101 **Ionescu A**, Dufresne F, Gelbcke M, Jabin I, Kiss R, Lamoral-Theys D. DYRK1A kinase inhibitors with emphasis on cancer. *Mini Rev Med Chem* 2012; **12**: 1315-1329 [PMID: 23016545 DOI: 10.2174/13895575112091315]
- 102 **Pozo N**, Zahonero C, Fernández P, Liñares JM, Ayuso A, Hagiwara M, Pérez A, Ricoy JR, Hernández-Lain A, Sepúlveda JM, Sánchez-Gómez P. Inhibition of DYRK1A destabilizes EGFR and reduces EGFR-dependent glioblastoma growth. *J Clin Invest* 2013; **123**: 2475-2487 [PMID: 23635774 DOI: 10.1172/JCI63623]
- 103 **Liu Q**, Liu N, Zang S, Liu H, Wang P, Ji C, Sun X. Tumor suppressor DYRK1A effects on proliferation and chemoresistance of AML cells by downregulating c-Myc. *PLoS One* 2014; **9**: e98853 [PMID: 24901999 DOI: 10.1371/journal.pone.0098853]
- 104 **Fernández-Martínez P**, Zahonero C, Sánchez-Gómez P. DYRK1A: the double-edged kinase as a protagonist in cell growth and tumorigenesis. *Mol Cell Oncol* 2015; **2**: e970048 [PMID: 27308401 DOI: 10.4161/23723548.2014.970048]
- 105 **Abbassi R**, Johns TG, Kassiou M, Munoz L. DYRK1A in neurodegeneration and cancer: Molecular basis and clinical implications. *Pharmacol Ther* 2015; **151**: 87-98 [PMID: 25795597 DOI: 10.1016/j.pharmthera.2015.03.004]
- 106 **Radhakrishnan A**, Nanjappa V, Raja R, Sathe G, Puttamallesh VN, Jain AP, Pinto SM, Balaji SA, Chavan S, Sahasrabudhe NA, Mathur PP, Kumar MM, Prasad TS, Santosh V, Sukumar G, Califano JA, Rangarajan A, Sidransky D, Pandey A, Gowda H, Chatterjee A. A dual specificity kinase, DYRK1A, as a potential therapeutic target for head and neck squamous cell carcinoma. *Sci Rep* 2016; **6**: 36132 [PMID: 27796319 DOI: 10.1038/srep36132]
- 107 **Zou Y**, Yao S, Chen X, Liu D, Wang J, Yuan X, Rao J, Xiong H, Yu S, Yuan X, Zhu F, Hu G,

- Wang Y, Xiong H. LncRNA OIP5-AS1 regulates radioresistance by targeting DYRK1A through miR-369-3p in colorectal cancer cells. *Eur J Cell Biol* 2018; **97**: 369-378 [PMID: 29773344 DOI: 10.1016/j.ejcb.2018.04.005]
- 108 **Jarhad DB**, Mashelkar KK, Kim HR, Noh M, Jeong LS. Dual-Specificity Tyrosine Phosphorylation-Regulated Kinase 1A (DYRK1A) Inhibitors as Potential Therapeutics. *J Med Chem* 2018; **61**: 9791-9810 [PMID: 29985601 DOI: 10.1021/acs.jmedchem.8b00185]
- 109 **Luna J**, Boni J, Cuatrecasas M, Bofill-De Ros X, Núñez-Manchón E, Gironella M, Vaquero EC, Arbones ML, de la Luna S, Fillat C. DYRK1A modulates c-MET in pancreatic ductal adenocarcinoma to drive tumour growth. *Gut* 2019; **68**: 1465-1476 [PMID: 30343272 DOI: 10.1136/gutjnl-2018-316128]
- 110 **Szamborska-Gbur A**, Rutkowska E, Dreasa A, Frid M, Vilenchik M, Milik M, Brzózka K, Król M. How to design potent and selective DYRK1B inhibitors? *J Mol Model* 2019; **25**: 41 [PMID: 30673861 DOI: 10.1007/s00894-018-3921-3]
- 111 **Mohyeldin A**, Garzón-Muvdi T, Quiñones-Hinojosa A. Oxygen in stem cell biology: a critical component of the stem cell niche. *Cell Stem Cell* 2010; **7**: 150-161 [PMID: 20682444 DOI: 10.1016/j.stem.2010.07.007]
- 112 **Mimeault M**, Batra SK. Hypoxia-inducing factors as master regulators of stemness properties and altered metabolism of cancer- and metastasis-initiating cells. *J Cell Mol Med* 2013; **17**: 30-54 [PMID: 23301832 DOI: 10.1111/jcmm.12004]
- 113 **Zhou Y**, Fan W, Xiao Y. The effect of hypoxia on the stemness and differentiation capacity of PDLc and DPC. *Biomed Res Int* 2014; **2014**: 890675 [PMID: 24701587 DOI: 10.1155/2014/890675]
- 114 **Watkins DN**, Berman DM, Burkholder SG, Wang B, Beachy PA, Baylin SB. Hedgehog signalling within airway epithelial progenitors and in small-cell lung cancer. *Nature* 2003; **422**: 313-317 [PMID: 12629553 DOI: 10.1038/nature01493]
- 115 **Berman DM**, Karhadkar SS, Maitra A, Montes De Oca R, Gerstenblith MR, Briggs K, Parker AR, Shimada Y, Eshleman JR, Watkins DN, Beachy PA. Widespread requirement for Hedgehog ligand stimulation in growth of digestive tract tumours. *Nature* 2003; **425**: 846-851 [PMID: 14520411 DOI: 10.1038/nature01972]
- 116 **Thayer SP**, di Magliano MP, Heiser PW, Nielsen CM, Roberts DJ, Lauwers GY, Qi YP, Gysin S, Fernández-del Castillo C, Yajnik V, Antoniu B, McMahon M, Warshaw AL, Hebrok M. Hedgehog is an early and late mediator of pancreatic cancer tumorigenesis. *Nature* 2003; **425**: 851-856 [PMID: 14520413 DOI: 10.1038/nature02009]
- 117 **Rubin LL**, de Sauvage FJ. Targeting the Hedgehog pathway in cancer. *Nat Rev Drug Discov* 2006; **5**: 1026-1033 [PMID: 17139287 DOI: 10.1038/nrd2086]
- 118 **Stecca B**, Mas C, Clement V, Zbinden M, Correa R, Piguet V, Beermann F, Ruiz i Altaba A. Melanomas require HEDGEHOG-GLI signaling regulated by interactions between GLI1 and the RAS-MEK/AKT pathways. *Proc Natl Acad Sci USA* 2007; **104**: 5895-5900 [PMID: 17392427 DOI: 10.1073/pnas.0700776104]
- 119 **Lauth M**, Bergström A, Shimokawa T, Tostar U, Jin Q, Fendrich V, Guerra C, Barbacid M, Toftgård R. DYRK1B-dependent autocrine-to-paracrine shift of Hedgehog signaling by mutant RAS. *Nat Struct Mol Biol* 2010; **17**: 718-725 [PMID: 20512148 DOI: 10.1038/nsmb.1833]
- 120 **Briscoe J**, Théron PP. The mechanisms of Hedgehog signalling and its roles in development and disease. *Nat Rev Mol Cell Biol* 2013; **14**: 416-429 [PMID: 23719536 DOI: 10.1038/nrm3598]
- 121 **Gruber W**, Hutzinger M, Elmer DP, Parigger T, Sternberg C, Cegielski L, Zaja M, Leban J, Michel S, Hamm S, Vitt D, Aberger F. DYRK1B as therapeutic target in Hedgehog/GLI-dependent cancer cells with Smoothed inhibitor resistance. *Oncotarget* 2016; **7**: 7134-7148 [PMID: 26784250 DOI: 10.18632/oncotarget.6910]
- 122 **Ingham PW**, Nakano Y, Seger C. Mechanisms and functions of Hedgehog signalling across the metazoa. *Nat Rev Genet* 2011; **12**: 393-406 [PMID: 21502959 DOI: 10.1038/nrg2984]
- 123 **Hui CC**, Angers S. Gli proteins in development and disease. *Annu Rev Cell Dev Biol* 2011; **27**: 513-537 [PMID: 21801010 DOI: 10.1146/annurev-cellbio-092910-154048]
- 124 **Aberger F**, Ruiz i Altaba A. Context-dependent signal integration by the GLI code: the oncogenic load, pathways, modifiers and implications for cancer therapy. *Semin Cell Dev Biol* 2014; **33**: 93-104 [PMID: 24852887 DOI: 10.1016/j.semdb.2014.05.003]
- 125 **Ramsbottom SA**, Pownall ME. Regulation of Hedgehog Signalling Inside and Outside the Cell. *J Dev Biol* 2016; **4**: 23 [PMID: 27547735 DOI: 10.3390/jdb4030023]
- 126 **Belgacem YH**, Hamilton AM, Shim S, Spencer KA, Borodinsky LN. The Many Hats of Sonic Hedgehog Signaling in Nervous System Development and Disease. *J Dev Biol* 2016; **4** [PMID: 29615598 DOI: 10.3390/jdb4040035]
- 127 **Fernandes-Silva H**, Correia-Pinto J, Moura RS. Canonical Sonic Hedgehog Signaling in Early Lung Development. *J Dev Biol* 2017; **5** [PMID: 29615561 DOI: 10.3390/jdb5010003]
- 128 **Pandit T**, Ogden SK. Contributions of Noncanonical Smoothed Signaling During Embryonic Development. *J Dev Biol* 2017; **5** [PMID: 29399514 DOI: 10.3390/jdb5040011]
- 129 **Wang B**, Fallon JF, Beachy PA. Hedgehog-regulated processing of Gli3 produces an anterior/posterior repressor gradient in the developing vertebrate limb. *Cell* 2000; **100**: 423-434 [PMID: 10693759 DOI: 10.1016/S0092-8674(00)80678-9]
- 130 **Riobó NA**, Lu K, Ai X, Haines GM, Emerson CP Jr. Phosphoinositide 3-kinase and Akt are essential for Sonic Hedgehog signaling. *Proc Natl Acad Sci USA* 2006; **103**: 4505-4510 [PMID:

- 16537363 DOI: [10.1073/pnas.0504337103](https://doi.org/10.1073/pnas.0504337103)]
- 131 **Pasca di Magliano M**, Sekine S, Ermilov A, Ferris J, Dlugosz AA, Hebrok M. Hedgehog/Ras interactions regulate early stages of pancreatic cancer. *Genes Dev* 2006; **20**: 3161-3173 [PMID: [17114586](https://pubmed.ncbi.nlm.nih.gov/17114586/) DOI: [10.1101/gad.1470806](https://doi.org/10.1101/gad.1470806)]
- 132 **Morton JP**, Mongeau ME, Klimstra DS, Morris JP, Lee YC, Kawaguchi Y, Wright CV, Hebrok M, Lewis BC. Sonic hedgehog acts at multiple stages during pancreatic tumorigenesis. *Proc Natl Acad Sci U S A* 2007; **104**: 5103-5108 [PMID: [17372229](https://pubmed.ncbi.nlm.nih.gov/17372229/) DOI: [10.1073/pnas.0701158104](https://doi.org/10.1073/pnas.0701158104)]
- 133 **Lauth M**, Bergström A, Toftgård R. Phorbol esters inhibit the Hedgehog signalling pathway downstream of Suppressor of Fused, but upstream of Gli. *Oncogene* 2007; **26**: 5163-5168 [PMID: [17310984](https://pubmed.ncbi.nlm.nih.gov/17310984/) DOI: [10.1038/sj.onc.1210321](https://doi.org/10.1038/sj.onc.1210321)]
- 134 **Chen Y**, Yue S, Xie L, Pu XH, Jin T, Cheng SY. Dual Phosphorylation of suppressor of fused (Sufu) by PKA and GSK3beta regulates its stability and localization in the primary cilium. *J Biol Chem* 2011; **286**: 13502-13511 [PMID: [21317289](https://pubmed.ncbi.nlm.nih.gov/21317289/) DOI: [10.1074/jbc.M110.217604](https://doi.org/10.1074/jbc.M110.217604)]
- 135 **Wang Y**, Ding Q, Yen CJ, Xia W, Izzo JG, Lang JY, Li CW, Hsu JL, Miller SA, Wang X, Lee DF, Hsu JM, Huo L, Labaff AM, Liu D, Huang TH, Lai CC, Tsai FJ, Chang WC, Chen CH, Wu TT, Buttar NS, Wang KK, Wu Y, Wang H, Ajani J, Hung MC. The crosstalk of mTOR/S6K1 and Hedgehog pathways. *Cancer Cell* 2012; **21**: 374-387 [PMID: [22439934](https://pubmed.ncbi.nlm.nih.gov/22439934/) DOI: [10.1016/j.ccr.2011.12.028](https://doi.org/10.1016/j.ccr.2011.12.028)]
- 136 **Klein C**, Zwick A, Kissel S, Forster CU, Pfeifer D, Follo M, Illert AL, Decker S, Benkler T, Pahl H, Oostendorp RA, Aumann K, Duyster J, Dierks C. Pth2 Loss drives myeloproliferation and myeloproliferative neoplasm progression. *J Exp Med* 2016; **213**: 273-290 [PMID: [26834157](https://pubmed.ncbi.nlm.nih.gov/26834157/) DOI: [10.1084/jem.20150556](https://doi.org/10.1084/jem.20150556)]
- 137 **Singh R**, Dhanyamraju PK, Lauth M. DYRK1B blocks canonical and promotes non-canonical Hedgehog signaling through activation of the mTOR/AKT pathway. *Oncotarget* 2017; **8**: 833-845 [PMID: [27903983](https://pubmed.ncbi.nlm.nih.gov/27903983/) DOI: [10.18632/oncotarget.13662](https://doi.org/10.18632/oncotarget.13662)]
- 138 **Montagnani V**, Stecca B. Role of Protein Kinases in Hedgehog Pathway Control and Implications for Cancer Therapy. *Cancers (Basel)* 2019; **11** [PMID: [30934935](https://pubmed.ncbi.nlm.nih.gov/30934935/) DOI: [10.3390/cancers11040449](https://doi.org/10.3390/cancers11040449)]
- 139 **Buonamici S**, Williams J, Morrissey M, Wang A, Guo R, Vattay A, Hsiao K, Yuan J, Green J, Ospina B, Yu Q, Ostrom L, Fordjour P, Anderson DL, Monahan JE, Kelleher JF, Peukert S, Pan S, Wu X, Maira SM, García-Echeverría C, Briggs KJ, Watkins DN, Yao YM, Lengauer C, Warmuth M, Sellers WR, Dorsch M. Interfering with resistance to smoothened antagonists by inhibition of the PI3K pathway in medulloblastoma. *Sci Transl Med* 2010; **2**: 51ra70 [PMID: [20881279](https://pubmed.ncbi.nlm.nih.gov/20881279/) DOI: [10.1126/scitranslmed.3001599](https://doi.org/10.1126/scitranslmed.3001599)]
- 140 **Kebenko M**, Drenckhan A, Gros SJ, Jücker M, Grabinski N, Ewald F, Grottke A, Schultze A, Izbicki JR, Bokemeyer C, Wellbrock J, Fiedler W. ErbB2 signaling activates the Hedgehog pathway via PI3K-Akt in human esophageal adenocarcinoma: identification of novel targets for concerted therapy concepts. *Cell Signal* 2015; **27**: 373-381 [PMID: [25435423](https://pubmed.ncbi.nlm.nih.gov/25435423/) DOI: [10.1016/j.cellsig.2014.11.022](https://doi.org/10.1016/j.cellsig.2014.11.022)]
- 141 **Mao J**, Maye P, Kogerman P, Tejedor FJ, Toftgård R, Xie W, Wu G, Wu D. Regulation of Gli1 transcriptional activity in the nucleus by Dyrk1. *J Biol Chem* 2002; **277**: 35156-35161 [PMID: [12138125](https://pubmed.ncbi.nlm.nih.gov/12138125/) DOI: [10.1074/jbc.M206743200](https://doi.org/10.1074/jbc.M206743200)]
- 142 **Shimokawa T**, Tostar U, Lauth M, Palaniswamy R, Kasper M, Toftgård R, Zaphiropoulos PG. Novel human glioma-associated oncogene 1 (GLI1) splice variants reveal distinct mechanisms in the terminal transduction of the hedgehog signal. *J Biol Chem* 2008; **283**: 14345-14354 [PMID: [18378682](https://pubmed.ncbi.nlm.nih.gov/18378682/) DOI: [10.1074/jbc.M800299200](https://doi.org/10.1074/jbc.M800299200)]
- 143 **Schneider P**, Bayo-Fina JM, Singh R, Kumar Dhanyamraju P, Holz P, Baier A, Fendrich V, Ramaswamy A, Baumeister S, Martinez ED, Lauth M. Identification of a novel actin-dependent signal transducing module allows for the targeted degradation of GLI1. *Nat Commun* 2015; **6**: 8023 [PMID: [26310823](https://pubmed.ncbi.nlm.nih.gov/26310823/) DOI: [10.1038/ncomms9023](https://doi.org/10.1038/ncomms9023)]
- 144 **Ehe BK**, Lamson DR, Tarpley M, Onyenwoke RU, Graves LM, Williams KP. Identification of a DYRK1A-mediated phosphorylation site within the nuclear localization sequence of the hedgehog transcription factor GLI1. *Biochem Biophys Res Commun* 2017; **491**: 767-772 [PMID: [28735864](https://pubmed.ncbi.nlm.nih.gov/28735864/) DOI: [10.1016/j.bbrc.2017.07.107](https://doi.org/10.1016/j.bbrc.2017.07.107)]
- 145 **Varjosalo M**, Björklund M, Cheng F, Syvänen H, Kivioja T, Kilpinen S, Sun Z, Kallioniemi O, Stunnenberg HG, He WW, Ojala P, Taipale J. Application of active and kinase-deficient kinome collection for identification of kinases regulating hedgehog signaling. *Cell* 2008; **133**: 537-548 [PMID: [18455992](https://pubmed.ncbi.nlm.nih.gov/18455992/) DOI: [10.1016/j.cell.2008.02.047](https://doi.org/10.1016/j.cell.2008.02.047)]
- 146 **Galvin KE**, Ye H, Erstad DJ, Feddersen R, Wetmore C. Gli1 induces G2/M arrest and apoptosis in hippocampal but not tumor-derived neural stem cells. *Stem Cells* 2008; **26**: 1027-1036 [PMID: [18276799](https://pubmed.ncbi.nlm.nih.gov/18276799/) DOI: [10.1634/stemcells.2007-0879](https://doi.org/10.1634/stemcells.2007-0879)]
- 147 **Schubbert S**, Shannon K, Bollag G. Hyperactive Ras in developmental disorders and cancer. *Nat Rev Cancer* 2007; **7**: 295-308 [PMID: [17384584](https://pubmed.ncbi.nlm.nih.gov/17384584/) DOI: [10.1038/nrc2109](https://doi.org/10.1038/nrc2109)]
- 148 **Shi Y**, Chen J, Karner CM, Long F. Hedgehog signaling activates a positive feedback mechanism involving insulin-like growth factors to induce osteoblast differentiation. *Proc Natl Acad Sci USA* 2015; **112**: 4678-4683 [PMID: [25825734](https://pubmed.ncbi.nlm.nih.gov/25825734/) DOI: [10.1073/pnas.1502301112](https://doi.org/10.1073/pnas.1502301112)]
- 149 **Hickmott J**. DYRK1B variant linked to autosomal dominant metabolic syndrome. *Clin Genet* 2015; **87**: 30-31 [PMID: [25092113](https://pubmed.ncbi.nlm.nih.gov/25092113/) DOI: [10.1111/cge.12477](https://doi.org/10.1111/cge.12477)]
- 150 **Ortega-Molina A**, Lopez-Guadamillas E, Mattison JA, Mitchell SJ, Muñoz-Martín M, Iglesias G, Gutierrez VM, Vaughan KL, Szarowicz MD, González-García I, López M, Cebrián D, Martínez S,

- Pastor J, de Cabo R, Serrano M. Pharmacological inhibition of PI3K reduces adiposity and metabolic syndrome in obese mice and rhesus monkeys. *Cell Metab* 2015; **21**: 558-570 [PMID: 25817535 DOI: 10.1016/j.cmet.2015.02.017]
- 151 **Singh R**, Holz PS, Roth K, Hupfer A, Meissner W, Müller R, Buchholz M, Gress TM, Elsässer HP, Jacob R, Lauth M. DYRK1B regulates Hedgehog-induced microtubule acetylation. *Cell Mol Life Sci* 2019; **76**: 193-207 [PMID: 30317528 DOI: 10.1007/s00018-018-2942-5]
- 152 **Zou Y**, Lim S, Lee K, Deng X, Friedman E. Serine/threonine kinase Mirk/Dyrk1B is an inhibitor of epithelial cell migration and is negatively regulated by the Met adaptor Ran-binding protein M. *J Biol Chem* 2003; **278**: 49573-49581 [PMID: 14500717 DOI: 10.1074/jbc.M307556200]
- 153 **Wang D**, Li Z, Messing EM, Wu G. Activation of Ras/Erk pathway by a novel MET-interacting protein RanBPM. *J Biol Chem* 2002; **277**: 36216-36222 [PMID: 12147692 DOI: 10.1074/jbc.M205111200]
- 154 **Collins CS**, Hong J, Sapinoso L, Zhou Y, Liu Z, Micklash K, Schultz PG, Hampton GM. A small interfering RNA screen for modulators of tumor cell motility identifies MAP4K4 as a promigratory kinase. *Proc Natl Acad Sci USA* 2006; **103**: 3775-3780 [PMID: 16537454 DOI: 10.1073/pnas.0600040103]
- 155 **Ashford AL**, Dunkley TP, Cockerill M, Rowlinson RA, Baak LM, Gallo R, Balmanno K, Goodwin LM, Ward RA, Lochhead PA, Guichard S, Hudson K, Cook SJ. Identification of DYRK1B as a substrate of ERK1/2 and characterisation of the kinase activity of DYRK1B mutants from cancer and metabolic syndrome. *Cell Mol Life Sci* 2016; **73**: 883-900 [PMID: 26346493 DOI: 10.1007/s00018-015-2032-x]
- 156 **Hong SH**, Lee KS, Kwak SJ, Kim AK, Bai H, Jung MS, Kwon OY, Song WJ, Tatar M, Yu K. Minibrain/Dyrk1a regulates food intake through the Sir2-FOXO-sNPF/NPY pathway in Drosophila and mammals. *PLoS Genet* 2012; **8**: e1002857 [PMID: 22876196 DOI: 10.1371/journal.pgen.1002857]
- 157 **Kha HT**, Basseri B, Shouhed D, Richardson J, Tetradis S, Hahn TJ, Parhami F. Oxysterols regulate differentiation of mesenchymal stem cells: pro-bone and anti-fat. *J Bone Miner Res* 2004; **19**: 830-840 [PMID: 15068507 DOI: 10.1359/JBMR.040115]
- 158 **Johnson JS**, Meliton V, Kim WK, Lee KB, Wang JC, Nguyen K, Yoo D, Jung ME, Atti E, Tetradis S, Pereira RC, Magyar C, Nargizyan T, Hahn TJ, Farouz F, Thies S, Parhami F. Novel oxysterols have pro-osteogenic and anti-adipogenic effects *in vitro* and induce spinal fusion *in vivo*. *J Cell Biochem* 2011; **112**: 1673-1684 [PMID: 21503957 DOI: 10.1002/jcb.23082]
- 159 **Nosavanh L**, Yu DH, Jaehnig EJ, Tong Q, Shen L, Chen MH. Cell-autonomous activation of Hedgehog signaling inhibits brown adipose tissue development. *Proc Natl Acad Sci U S A* 2015; **112**: 5069-5074 [PMID: 25848030 DOI: 10.1073/pnas.1420978112]
- 160 **Borycki A**, Brown AM, Emerson CP Jr. Shh and Wnt signaling pathways converge to control Gli gene activation in avian somites. *Development* 2000; **127**: 2075-2087 [PMID: 10769232]
- 161 **Shi Y**, Long F. Hedgehog signaling *via* Gli2 prevents obesity induced by high-fat diet in adult mice. *Elife* 2017; **6** [PMID: 29205155 DOI: 10.7554/eLife.31649]
- 162 **Christodoulides C**, Lagathu C, Sethi JK, Vidal-Puig A. Adipogenesis and WNT signalling. *Trends Endocrinol Metab* 2009; **20**: 16-24 [PMID: 19008118 DOI: 10.1016/j.tem.2008.09.002]
- 163 **Yun J**, Rago C, Cheong I, Pagliarini R, Angenendt P, Rajagopalan H, Schmidt K, Willson JK, Markowitz S, Zhou S, Diaz LA Jr, Velculescu VE, Lengauer C, Kinzler KW, Vogelstein B, Papadopoulos N. Glucose deprivation contributes to the development of KRAS pathway mutations in tumor cells. *Science* 2009; **325**: 1555-1559 [PMID: 19661383 DOI: 10.1126/science.1174229]
- 164 **Feng B**, Jiao P, Yang Z, Xu H. MEK/ERK pathway mediates insulin-promoted degradation of MKP-3 protein in liver cells. *Mol Cell Endocrinol* 2012; **361**: 116-123 [PMID: 22521266 DOI: 10.1016/j.mce.2012.03.025]
- 165 **Yin H**, Price F, Rudnicki MA. Satellite cells and the muscle stem cell niche. *Physiol Rev* 2013; **93**: 23-67 [PMID: 23303905 DOI: 10.1152/physrev.00043.2011]
- 166 **Koleva M**, Kappler R, Vogler M, Herwig A, Fulda S, Hahn H. Pleiotropic effects of sonic hedgehog on muscle satellite cells. *Cell Mol Life Sci* 2005; **62**: 1863-1870 [PMID: 16003493 DOI: 10.1007/s00018-005-5072-9]
- 167 **Kern D**, Regl G, Hofbauer SW, Altenhofer P, Achatz G, Dlugosz A, Schnidar H, Greil R, Hartmann TN, Aberger F. Hedgehog/GLI and PI3K signaling in the initiation and maintenance of chronic lymphocytic leukemia. *Oncogene* 2015; **34**: 5341-5351 [PMID: 25639866 DOI: 10.1038/onc.2014.450]
- 168 **Garrett S**, Menold MM, Broach JR. The *Saccharomyces cerevisiae* YAK1 gene encodes a protein kinase that is induced by arrest early in the cell cycle. *Mol Cell Biol* 1991; **11**: 4045-4052 [PMID: 2072907 DOI: 10.1128/mcb.11.8.4045]
- 169 **Taminato A**, Bagattini R, Gorjão R, Chen G, Kuspa A, Souza GM. Role for Yaka, cAMP, and protein kinase A in regulation of stress responses of Dictyostelium discoideum cells. *Mol Biol Cell* 2002; **13**: 2266-2275 [PMID: 12134067 DOI: 10.1091/mbc.01-11-0555]
- 170 **Meistrich M**, van Beek M. Spermatogonial stem cells. In: Desjardins C, Ewing LL (Hrsg.). Cell and Molecular Biology of the Testis. New York: Oxford University Press, 1993: 266-295
- 171 **Oatley JM**, Brinster RL. Spermatogonial stem cells. *Methods Enzymol* 2006; **419**: 259-282 [PMID: 17141059 DOI: 10.1016/S0076-6879(06)19011-4]
- 172 **Nakagawa T**, Sharma M, Nabeshima Y, Braun RE, Yoshida S. Functional hierarchy and reversibility within the murine spermatogenic stem cell compartment. *Science* 2010; **328**: 62-67

- [PMID: 20299552 DOI: 10.1126/science.1182868]
- 173 **Fujita J.** Cold shock response in mammalian cells. *J Mol Microbiol Biotechnol* 1999; **1**: 243-255 [PMID: 10943555]
- 174 **Yang C,** Carrier F. The UV-inducible RNA-binding protein A18 (A18 hnRNP) plays a protective role in the genotoxic stress response. *J Biol Chem* 2001; **276**: 47277-47284 [PMID: 11574538 DOI: 10.1074/jbc.M105396200]
- 175 **Wellmann S,** Bühler C, Moderegger E, Zelmer A, Kirschner R, Koehne P, Fujita J, Seeger K. Oxygen-regulated expression of the RNA-binding proteins RBM3 and CIRP by a HIF-1-independent mechanism. *J Cell Sci* 2004; **117**: 1785-1794 [PMID: 15075239 DOI: 10.1242/jcs.01026]
- 176 **Yang R,** Weber DJ, Carrier F. Post-transcriptional regulation of thioredoxin by the stress inducible heterogenous ribonucleoprotein A18. *Nucleic Acids Res* 2006; **34**: 1224-1236 [PMID: 16513844 DOI: 10.1093/nar/gkj519]
- 177 **De Leeuw F,** Zhang T, Wauquier C, Huez G, Krays V, Gueydan C. The cold-inducible RNA-binding protein migrates from the nucleus to cytoplasmic stress granules by a methylation-dependent mechanism and acts as a translational repressor. *Exp Cell Res* 2007; **313**: 4130-4144 [PMID: 17967451 DOI: 10.1016/j.yexcr.2007.09.017]
- 178 **Nishiyama H,** Danno S, Kaneko Y, Itoh K, Yokoi H, Fukumoto M, Okuno H, Millán JL, Matsuda T, Yoshida O, Fujita J. Decreased expression of cold-inducible RNA-binding protein (CIRP) in male germ cells at elevated temperature. *Am J Pathol* 1998; **152**: 289-296 [PMID: 9422546 DOI: 10.1097/00005392-199904020-00373]
- 179 **Leonart ME.** A new generation of proto-oncogenes: cold-inducible RNA binding proteins. *Biochim Biophys Acta* 2010; **1805**: 43-52 [PMID: 19900510 DOI: 10.1016/j.bbcan.2009.11.001]
- 180 **Jessell TM.** Neuronal specification in the spinal cord: inductive signals and transcriptional codes. *Nat Rev Genet* 2000; **1**: 20-29 [PMID: 11262869 DOI: 10.1038/35049541]
- 181 **Marquardt T,** Pfaff SL. Cracking the transcriptional code for cell specification in the neural tube. *Cell* 2001; **106**: 651-654 [PMID: 11572771 DOI: 10.1016/s0092-8674(01)00499-8]
- 182 **Götz M,** Huttner WB. The cell biology of neurogenesis. *Nat Rev Mol Cell Biol* 2005; **6**: 777-788 [PMID: 16314867 DOI: 10.1038/nrm1739]
- 183 **Götz M,** Nakafuku M, Petrik D. Neurogenesis in the Developing and Adult Brain-Similarities and Key Differences. *Cold Spring Harb Perspect Biol* 2016; **8** [PMID: 27235475 DOI: 10.1101/cshperspect.a018853]
- 184 **Zhong W,** Chia W. Neurogenesis and asymmetric cell division. *Curr Opin Neurobiol* 2008; **18**: 4-11 [PMID: 18513950 DOI: 10.1016/j.conb.2008.05.002]
- 185 **Hardwick LJ,** Ali FR, Azzarelli R, Philpott A. Cell cycle regulation of proliferation vs differentiation in the central nervous system. *Cell Tissue Res* 2015; **359**: 187-200 [PMID: 24859217 DOI: 10.1007/s00441-014-1895-8]
- 186 **Ohnuma S,** Harris WA. Neurogenesis and the cell cycle. *Neuron* 2003; **40**: 199-208 [PMID: 14556704 DOI: 10.1016/S0896-6273(03)00632-9]
- 187 **Nguyen L,** Besson A, Roberts JM, Guillemot F. Coupling cell cycle exit, neuronal differentiation and migration in cortical neurogenesis. *Cell Cycle* 2006; **5**: 2314-2318 [PMID: 17102618 DOI: 10.4161/cc.5.20.3381]
- 188 **Politis PK,** Thomaidou D, Matsas R. Coordination of cell cycle exit and differentiation of neuronal progenitors. *Cell Cycle* 2008; **7**: 691-697 [PMID: 18239460 DOI: 10.4161/cc.7.6.5550]
- 189 **Pitto L,** Cremisi F. Timing neurogenesis by cell cycle? *Cell Cycle* 2010; **9**: 434-435 [PMID: 20090420 DOI: 10.4161/cc.9.3.10762]
- 190 **Altafaj X,** Dierssen M, Baamonde C, Martí E, Visa J, Guimera J, Oset M, González JR, Flórez J, Fillat C, Estivill X. Neurodevelopmental delay, motor abnormalities and cognitive deficits in transgenic mice overexpressing Dyrk1A (minibrain), a murine model of Down's syndrome. *Hum Mol Genet* 2001; **10**: 1915-1923 [PMID: 11555628 DOI: 10.1093/hmg/10.18.1915]
- 191 **Bronicki LM,** Redin C, Drunat S, Piton A, Lyons M, Passemard S, Baumann C, Faivre L, Thevenon J, Rivière JB, Isidor B, Gan G, Francannet C, Willems M, Gunel M, Jones JR, Gleeson JG, Mandel JL, Stevenson RE, Friez MJ, Aylsworth AS. Ten new cases further delineate the syndromic intellectual disability phenotype caused by mutations in DYRK1A. *Eur J Hum Genet* 2015; **23**: 1482-1487 [PMID: 25920557 DOI: 10.1038/ejhg.2015.29]
- 192 **Duchon A,** Herault Y. DYRK1A, a Dosage-Sensitive Gene Involved in Neurodevelopmental Disorders, Is a Target for Drug Development in Down Syndrome. *Front Behav Neurosci* 2016; **10**: 104 [PMID: 27375444 DOI: 10.3389/fnbeh.2016.00104]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

