Emerging role of DYRK1A as a target in cardiovascular diseases (Review)

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Abstract. Cardiovascular diseases (CVDs) remain the leading cause of global mortality, imposing a substantial burden on public health. Dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) is a conserved protein kinase involved in diverse biological processes, and its aberrant expression has been associated with multiple human diseases. Emerging evidence indicates that DYRK1A contributes to the pathogenesis of various CVDs. However, its context-specific regulatory mechanisms and therapeutic potential in CVDs remain insufficiently characterized, limiting the development of targeted interventions. This review summarizes the roles of DYRK1A in three major CVDs: Myocardial infarction (MI), cardiomyocyte hypertrophy and pulmonary arterial hypertension (PAH) In MI, DYRK1A inhibits cardiomyocyte proliferation by suppressing cell cycle-associated signaling pathways, including the retinoblastoma protein/E2f pathway, and modulating epigenetic mechanisms, thereby impairing cardiac repair. In cardiomyocyte hypertrophy, DYRK1A inhibits abnormal myocardial growth by antagonizing pro-hypertrophic nuclear factor of activated T cells (NFAT) signaling via direct NFAT phosphorylation. In PAH, DYRK1A promotes pathological vascular remodeling by inducing pulmonary arterial smooth muscle cell hyperproliferation via the STAT3/Pim-1/NFAT pathway and impairing endothelial cell function via the DYRK1A/peroxisome proliferator-activated receptor γ/early growth response protein 1 pathway. The present review outlines the context-dependent regulatory effects of DYRK1A in CVDs, which are either protective or pathogenic depending on the disease type and stage. In addition, it emphasizes the requirement for further mechanistic evaluation and the development of DYRK1A-targeted strategies to advance the translational of DYRK1A as a disease-specific therapeutic target in CVDs.

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Contents

1. Introduction

Cardiovascular diseases (CVDs), including atherosclerosis, myocardial infarction (MI), heart failure (HF), myocardial hypertrophy, myocardial fibrosis, arrhythmia and hypertension, remain the leading cause of global mortality. The Global Burden of Cardiovascular Diseases Collaboration reported that an estimated ~19.8 million individuals succumbed to CVDs in 2022 (1). These chronic conditions arise from multiple risk factors, including diabetes, obesity, inflammation, elevated blood pressure, poor lifestyle habits and genetic predisposition (2-5). Achieving improvements in CVD diagnosis and treatment is hindered by limited understanding of the underlying pathogenesis, particularly the molecular mechanisms driving the dysfunction of cardiovascular system cells, such as smooth muscle cells (SMCs), endothelial cells (ECs), cardiomyocytes, inflammatory cells and fibroblasts, as well as abnormalities in signaling transduction and gene expression (6,7).

The dual-specificity tyrosine-regulated kinase (DYRK) family, a highly conserved group of proline-directed kinases within the cyclin-dependent kinase (CDK), mitogen-activated protein kinase, glycogen synthase kinase 3 and CDC-like kinase superfamily, plays important roles

in neuronal development, cell cycle regulation and mRNA splicing (8-12). DYRK members are classified into two classes based on sequence homology, as illustrated in Fig. 1. All DYRK proteins contain a conserved catalytic kinase domain and a DYRK homology (DH) box located upstream of the kinase domain (13). Among DYRK family members, DYRK1A is the most extensively studied, whereas DYRK1B, DYRK2, DYRK3 and DYRK4 have received less attention in cardiovascular research. DYRK1B primarily regulates skeletal muscle metabolism and tumor cell proliferation, with limited involvement in cardiac or vascular pathology (9). DYRK2 functions mainly in DNA damage repair and apoptosis; however, these roles have not been clearly associated with major CVD-associated processes, such as cardiomyocyte proliferation or pulmonary vascular remodeling (14). By contrast, DYRK1A has been demonstrated to be relevant to cardiovascular pathology. Located within the Down syndrome critical region on chromosome 21, both the upregulated and downregulated expression of DYRK1A have been associated with multiple human diseases, including cancer, Alzheimer's disease, diabetes, Down syndrome and CVDs (15-20). Unlike other DYRK family members, DYRK1A is widely expressed in the cardiovascular system, and its abnormal expression is consistently observed in CVDs, highlighting its potential as a cardiovascular therapeutic target.

A number of studies have demonstrated that DYRK1A is involved in regulating the onset and progression of CVDs; however, the underlying mechanisms in specific cardiovascular pathologies are as yet not fully understood (21-25). The present review summarizes recent findings regarding DYRK1A in the cardiovascular system, focusing on its structural characteristics, regulatory mechanisms and functional roles in major CVDs. By integrating current evidence, the review aims to clarify the relevance of DYRK1A to cardiovascular health and provide insights into potential DYRK1A-targeted therapeutic strategies.

A central concept addressed in this review is the context-dependent duality of DYRK1A, whereby it exerts opposing regulatory effects depending on disease context, cell type and disease stage. For example, DYRK1A suppresses pathological processes in cardiomyocyte hypertrophy but promotes disease progression in pulmonary arterial hypertension (PAH). In MI, DYRK1A appears to act as a detrimental regulator during the acute phase but may exhibit protective effects during chronic cardiac remodeling. This context-dependent behavior likely arises from its ability to interact with diverse downstream signaling pathways, respond to cell type-specific microenvironments and dynamically adapt to pathological stimuli. Recognition of this duality is essential for reconciling conflicting findings regarding DYRK1A function across different CVDs, and for guiding the development of precise, disease-specific therapeutic strategies targeting DYRK1A.

2. Structural characteristics of DYRK1A and brief regulatory insights

DYRK1A exerts diverse biological functions through the phosphorylation of >30 substrates involved in transcription, cell cycle progression, apoptosis, DNA damage repair and neuronal migration (26-31). As a dual-specificity kinase, it undergoes autophosphorylation, a property essential for its maturation and subsequent phosphorylation of downstream substrates to perform its regulatory functions (19,32,33).

The activity and functional specificity of DYRK1A are largely determined by its structural characteristics, which including several distinct structural regions. Consistent with all members of the DYRK family, DYRK1A contains a conserved catalytic kinase domain, with a DH box located immediately upstream. The catalytic domain includes Lys188, a critical residue that serves as the ATP-binding site and is indispensable for kinase activity (34). DYRK1A also contains two nuclear localization signals (NLSs), one upstream of the kinase domain and the other within it. These NLSs facilitate the nuclear translocation of DYRK1A, allowing it to phosphorylate nuclear substrates, such as nuclear factor of activated T cells (NFAT), a key regulator of myocardial hypertrophy, as well as transcription factors involved in cell cycle regulation. This nuclear localization is particularly important in cardiomyocytes, where DYRK1A directly modulates cell cycle progression and hypertrophic signaling (35).

In addition, DYRK1A contains a proline-, glutamic acid-, serine- and threonine-rich (PEST) domain that mediates protein degradation through the ubiquitin-proteasome system, enabling the dynamic regulation of its own protein levels in response to pathological stimuli, including myocardial ischemia and hypoxic stress in pulmonary vascular cells (36,37).

The N-terminus of DYRK1A contains a 13-consecutive histidine repeat region and serine/threonine-rich sequences. It has been demonstrated that the histidine-rich region promotes phase separation and the formation of liquid-like DYRK1A condensates (38). This process may increase the local concentration of DYRK1A and its substrates, thereby promoting the phosphorylation of targets such as D-cyclins, which regulate cardiomyocyte proliferation, and STAT3, which contributes to pulmonary arterial SMC hyperproliferation.

The phase separation capacity of DYRK1A likely contributes to its tissue-specific regulatory effects. In cardiomyocytes, phase separation-mediated substrate phosphorylation contributes to the inhibition of cell cycle progression, whereas in pulmonary vascular cells, it promotes pathological proliferation (39). These findings directly associate the structural properties of DYRK1A with its tissue-specific functional roles in cardiovascular pathologies.

The core enzymatic activation of DYRK1A is driven by the intramolecular cis-autophosphorylation of a conserved tyrosine residue, Tyr321, within the activation loop (A-loop) of its catalytic kinase domain. This process occurs co-translationally during ribosomal protein synthesis and folding, prior to the complete release of the nascent DYRK1A polypeptide (40).

Under physiological conditions, constitutively active DYRK1A is subjected to reversible inactivation and functional silencing through several complementary mechanisms, including reversible dephosphorylation of the A-loop, post-translational modification-mediated subcellular sequestration and PEST domain-dependent proteolytic degradation (41-43). Collectively, these mechanisms form a tightly regulated network that controls the spatiotemporal activity of DYRK1A in the cardiovascular system.

While cis-autophosphorylation ensures the constitutive enzymatic competence of DYRK1A, reversible inactivation

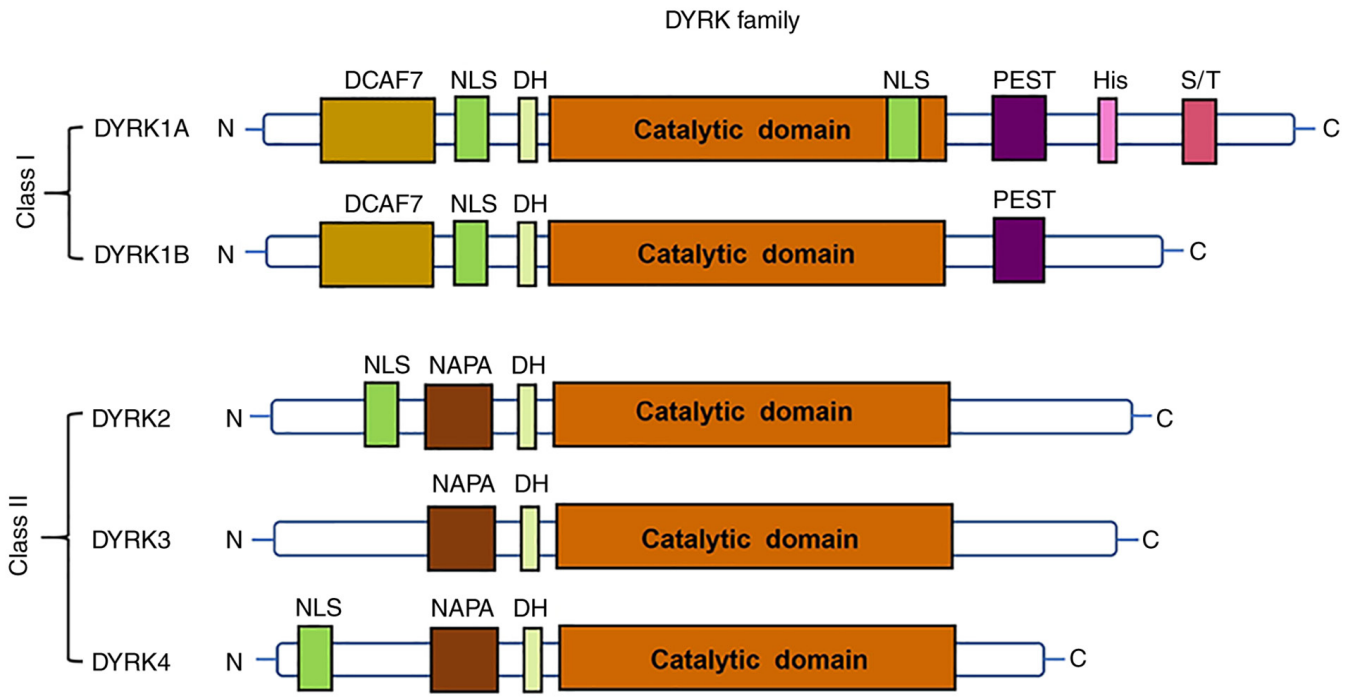

Figure 1. Structure of the DYRK family. DH, DYRK homology; DYRK, dual-specificity tyrosine phosphorylation-regulated kinase; His, histidine; NAPA, N-terminal autophosphorylation accessory; NLS, nuclear localization signal; PEST, proline-, glutamic acid-, serine- and threonine-rich; S/T, serine/threonine.

mechanisms including dephosphorylation, subcellular sequestration and proteolytic degradation regulate its functional activity. This is critical for the context-dependent regulatory roles of DYRK1A in cardiovascular pathologies such as cardiomyocyte hypertrophy and PAH.

3. DYRK1A in MI

MI is a life-threatening coronary disorder characterized by sudden and prolonged ischemia of myocardial tissue, leading to irreversible cardiomyocyte death (44,45). The primary cause of MI is the rupture or erosion of atherosclerotic plaques within the coronary arteries, which triggers thrombus formation and the subsequent occlusion of blood flow (46). This interruption of perfusion initiates a cascade of pathological events, including the release of pro-inflammatory cytokines, oxidative stress and mitochondrial dysfunction (47). Clinically, MI management prioritizes rapid reperfusion to restore coronary blood flow, while complementary pharmacological therapies are used to reduce myocardial oxygen demand (48). Despite advances in these interventions, MI remains a major global cause of morbidity and mortality. Therefore, the identification of molecular mechanisms and potential therapeutic targets remains essential for the development of improved treatment strategies.

A major limitation in post-MI cardiac recovery is the restricted regenerative capacity of the adult mammalian myocardium. Unlike lower vertebrates and neonatal mammals, adult mammals cannot effectively replenish the cardiomyocytes lost following MI-induced injury (49,50). Persistent cardiomyocyte loss promotes progressive ventricular remodeling and HF, significantly increasing mortality risk (51). Notably, increased cardiomyocyte proliferation has been found to be associated with improved left ventricular function after MI, suggesting that the stimulation of endogenous cardiomyocyte cell cycle activity represents a potential therapeutic strategy (52-54).

DYRK1A was originally identified to act as a regulator of tumor cell proliferation through the modulation of cell cycle-related proteins (55). However, it has since emerged as an important factor in cardiac repair following myocardial injury (56,57). A pivotal study using a mouse ischemia-reperfusion injury model demonstrated that the pharmacological inhibition or cardiomyocyte-specific deletion of DYRK1A improves cardiac function and increases cardiomyocyte cell cycle activity. These findings establish an association between DYRK1A and post-MI recovery, and highlight its therapeutic potential (56). Notably, the role of DYRK1A in post-MI repair is dynamic and phase-dependent, varying between the acute injury and chronic remodeling phases. This temporal specificity is critical for optimizing therapeutic benefit while minimizing adverse effects.

During the acute injury phase, which typically occurs within the first 72 h after MI, DYRK1A suppresses cardiomyocyte cell cycle progression through two principal mechanisms. First, DYRK1A directly phosphorylates core cell cycle regulators, including cyclin D1 and p27Kip1, thereby inhibiting the G_1/S phase transition. Second, DYRK1A interacts with chromatin remodeling complexes, such as histone deacetylase 4, to suppress the transcription of proliferation-promoting genes, including c-Myc and cyclin E1 (24,51,57,58). Pharmacological inhibition or cardiomyocyte-specific deletion of DYRK1A during this phase relieves cell cycle repression, promotes the proliferation of surviving cardiomyocytes and preserves early cardiac ejection fraction, demonstrating its therapeutic potential for acute MI (59).

In the chronic remodeling phase, which typically occurs ≥2 weeks after MI, DYRK1A participates in fibroblast activation and extracellular matrix (ECM) regulation. Inhibition of DYRK1A during this phase promotes transforming growth factor β (TGF-β)/Smad3 signaling, thereby increasing the differentiation of cardiac fibroblasts into myofibroblasts and increasing collagen deposition (57,59,60). This exacerbates ventricular stiffness and increases the risk of HF with preserved ejection fraction, indicating that targeting DYRK1A during the chronic phase may be detrimental and that phase-specific therapeutic strategies are required.

DYRK1A suppresses cardiomyocyte proliferation primarily through inhibition of the cell cycle. DYRK1A phosphorylates WD repeat domain 82 and lysine acetyltransferase 6A, thereby reducing the establishment of activating histone modifications, including histone H3 lysine 4 trimethylation and histone H3 lysine 27 acetylation, at the promoters of cell cycle regulatory genes (51). In addition, DYRK1A interacts with D-cyclin family members to reduce their protein levels. For example, DYRK1A overexpression increases the phosphorylation of cyclin D2, promoting its proteasomal degradation (24,61). DYRK1A also induces the hypophosphorylation of retinoblastoma protein 1 (Rb1), thereby suppressing the Rb/E2f signaling pathway and the transcription of E2f target genes. These mechanisms collectively result in G_1 phase arrest and the inhibition of cardiomyocyte cell cycle progression (24).

4. DYRK1A in cardiomyocyte hypertrophy

Cardiomyocyte hypertrophy is an adaptive response to diverse physiological or pathological stimuli, involving the enlargement of individual cardiomyocytes. Physiological hypertrophy is a beneficial adaptation to increased cardiac workload, such as during regular exercise, which enhances cardiac contractile function without compromising cardiac structure (59,62). By contrast, pathological hypertrophy is primarily triggered by chronic stressors, including hypertension, MI or genetic mutations, leading to the abnormal growth of adult cardiomyocytes, impaired contractility and pathological cardiac remodeling (63-65). Pathological cardiomyocyte hypertrophy is closely associated with reduced cardiac reserve, adverse clinical outcomes and an increased risk of HF and sudden cardiac death; therefore, it is widely recognized as a major predictor of cardiovascular morbidity and mortality (62).

A complex network of molecular signals regulates the development of cardiomyocyte hypertrophy. As a key component of the renin-angiotensin-aldosterone system, angiotensin II (Ang II) binds to the Ang II type 1 receptor, activating downstream pathways, including mitogen-activated protein kinase, phosphatidylinositol 3-kinase/Akt and calcium signaling pathways (66,67). These signaling cascades promote the synthesis of hypertrophy-associated proteins and ultimately increase cardiomyocyte size (68-70). In addition, catecholamines, including norepinephrine and epinephrine, interact with β-adrenergic receptors on cardiomyocytes, thereby activating G protein-coupled receptor signaling and protein kinase A, which promote the transcription of pro-hypertrophic genes, and contribute to cardiomyocyte hypertrophy and subsequent HF (71-73). Cytokine-mediated signaling pathways, including the TGF-β and tumor necrosis factor α pathways, also play important roles in the regulation of hypertrophic responses (74-76). Epigenetic mechanisms, including DNA methylation, histone modification and non-coding RNA-mediated regulation, have also emerged as key modulators of cardiomyocyte hypertrophy, further expanding understanding of its molecular basis (77,78).

Among the signaling pathways involved in cardiomyocyte hypertrophy, the calcium/calmodulin-activated phosphatase calcineurin and its downstream transcriptional effector, NFAT, represent a central regulatory axis (63,79). Under pro-hypertrophic conditions, calcineurin activation leads to NFAT dephosphorylation, enabling NFAT to translocate to the nucleus and facilitate the transcription of hypertrophy-associated genes (79). Consistent with this, genetic inhibition of calcineurin renders the heart unresponsive to a broad range of hypertrophic stimuli and attenuates pathological cardiac hypertrophy, highlighting the centrality of the calcineurin-NFAT axis in this process (80).

DYRK1A functions as a negative regulator of the calcineurin-NFAT signaling pathway through direct phosphorylation of the conserved Ser-Pro repeat-3 motif of nuclear NFAT, promoting its cytoplasmic re-localization and suppressing NFAT-mediated pro-hypertrophic transcriptional activity (30,59). However, conflicting findings have been reported regarding the regulatory role of DYRK1A in pathological hypertrophy. *In vitro* experiments using acute stimulation have demonstrated that DYRK1A overexpression inhibits NFAT activation and attenuates cardiomyocyte growth (18). By contrast, transgenic mouse models have indicated that myocardial DYRK1A overexpression does not suppress hypertrophy induced by transverse aortic constriction (TAC) or constitutively active calcineurin (25). These contrasting observations highlight the complexity of the DYRK1A-mediated regulation of cardiomyocyte hypertrophy, which may depend on the duration of pathological stress and the nature of hypertrophic stimuli.

DYRK1A-mediated acute signaling inhibition in hypertrophy. During acute hypertrophic stimuli, such as short-term Ang II exposure, DYRK1A exerts a rapid and direct inhibitory effect on pro-hypertrophic signaling. By phosphorylating nuclear NFAT, DYRK1A counteracts calcineurin-mediated NFAT dephosphorylation, thereby preventing the nuclear retention of NFAT and reducing the transcription of hypertrophic marker genes, including atrial natriuretic peptide and brain natriuretic peptide (18,59). This inhibition limits early cardiomyocyte enlargement and represents a direct NFAT-dependent regulatory role of DYRK1A. Such acute signaling inhibition has been consistently observed in short-term *in vitro* and *in vivo* experimental models.

Limited effect of DYRK1A on long-term hypertrophic remodeling. By contrast to its acute signaling effects, DYRK1A exhibits a diminished regulatory role during long-term pathological remodeling driven by chronic stress, such as sustained pressure overload induced by TAC. In chronic hypertrophy models, DYRK1A overexpression fails to prevent pathological ventricular remodeling, including cardiomyocyte hypertrophy, interstitial fibrosis and impaired cardiac contractility (25). This reduced efficacy may be attributed to the activation of

DYRK1A-resistant pro-hypertrophic pathways, which may function independently of the calcineurin-NFAT axis or involve alternative NFAT isoforms that are not effectively targeted by DYRK1A-mediated phosphorylation. In addition, chronic pressure overload may alter the subcellular localization, post-translational modification or protein-protein interactions of DYRK1A, thereby disrupting its NFAT-mediated inhibitory function (18). Collectively, these changes contribute to the inability of DYRK1A to suppress long-term hypertrophic remodeling despite sustained myocardial expression.

To reconcile the differences between acute and chronic effects, further research is necessary to identify DYRK1A-resistant signaling pathways involved in chronic hypertrophy and to determine whether chronic pathological stress induces adaptive changes in the regulatory function of DYRK1A. Insights obtained by such studies may aid in clarifying the context-dependent role of DYRK1A and support the development of therapeutic strategies that leverage its acute protective effects while overcoming resistance during long-term pathological remodeling.

5. DYRK1A in PAH

PAH is a progressive and heterogeneous disease defined by a resting mean pulmonary arterial pressure of ≥20 mmHg (81). Its pathogenesis is characterized by the pathological remodeling of pulmonary arteries, driven by abnormal proliferation of pulmonary artery SMCs (PASMCs), pulmonary EC dysfunction and excessive ECM deposition. These alterations increase vascular resistance, leading to chronic right ventricular (RV) pressure overload and eventual RV failure, which remains the primary cause of mortality in patients with PAH (82,83).

PAH is classified into heritable, environmental and comorbidity-associated subtypes. Heritable PAH is most commonly caused by mutations in bone morphogenetic protein receptor type 2 (BMPR2), which disrupt anti-proliferative BMP signaling (84-86). Environmental PAH is often triggered by chronic hypoxia, which induces the phenotypic switching of PASMCs into a hyperproliferative and apoptosis-resistant state (87-89). Comorbidity-associated PAH occurs in conditions such as rheumatoid arthritis, atrial septal defects, portal hypertension, acquired immunodeficiency syndrome and Down syndrome (90). Notably, Down syndrome, caused by trisomy 21, confers a significantly increased risk of PAH, largely due to pulmonary endothelial dysfunction (91).

DYRK1A is a key contributor to PAH pathogenesis, exerting cell-type-specific pathogenic effects through distinct signaling pathways in PASMCs and pulmonary ECs. In hypoxia-induced PAH, DYRK1A expression is upregulated in PASMCs and promotes hyperproliferation through the STAT3/Pim-1/NFAT pathway. DYRK1A phosphorylates STAT3, facilitating its nuclear translocation and promoting the transcription of Pim-1. Pim-1 subsequently stabilizes NFAT proteins, leading to the upregulated expression of genes associated with cell cycle progression, including cyclin D1, as well as anti-apoptotic factors, such as B cell lymphoma 2. These effects sustain PASMC hyperproliferation and apoptosis resistance, contributing to pulmonary vascular wall thickening (92).

In Down syndrome-associated PAH, DYRK1A overexpression driven by trisomy 21 disrupts pulmonary EC function through the DYRK1A/peroxisome proliferator-activated receptor γ (PPARG)/early growth response protein 1 (EGR1) pathway. DYRK1A phosphorylates PPARG, thereby impairing its DNA-binding ability and downstream gene activation. Reduced PPARG activity leads to increased EGR1 expression, which promotes the production of pro-inflammatory cytokines and pro-remodeling proteins. These molecular events impair endothelial angiogenesis, increase apoptosis, elevate mitochondrial reactive oxygen species and compromise endothelial integrity (93).

These cell-type-specific pathway activation effects are influenced by differential cofactor expression and pathway dependency. PASMCs exhibit hypoxia-induced upregulation of STAT3 and Pim-1, with limited EGR1 coactivator expression, whereas pulmonary ECs exhibit high basal PPARG expression and relatively limited NFAT signaling (92,93). These differences render each cell type responsive to distinct DYRK1A-mediated signaling pathways.

Harmine, a natural β-carboline alkaloid that targets the ATP-binding pocket of DYRK1A, has emerged as a potential therapeutic candidate for Down syndrome-associated PAH. Preclinical experiments using isogenic trisomy 21 and corrected disomy 21 induced pluripotent stem cell-derived ECs have shown that harmine reverses DYRK1A-mediated PPARG suppression, normalizes EGR1 levels and restores endothelial function (93). However, harmine exhibits off-target effects, including inhibition of DYRK1B, DYRK2 and CDK5, and may cause adverse effects such as neurotoxicity and gastrointestinal disturbances (94). In addition, the metabolism of harmine via cytochrome P450 family 1 subfamily A member 2 increases the risk of drug-drug interactions. These limitations highlight the requirement for structural optimization to improve DYRK1A selectivity, in addition to the development of targeted delivery strategies, such as EC-specific nanoparticle systems.

The cell-type specific role of DYRK1A in PASMCs and ECs underscores its potential as a therapeutic target for PAH. However, important gaps remain in understanding its interaction with key PAH pathways, particularly BMPR2 signaling. BMPR2 mutations are the most common cause of heritable PAH, and BMPR2 loss-of-function produces phenotypes comparable to those associated with DYRK1A overexpression, including PASMC hyperproliferation and EC dysfunction (84,95). Future studies should investigate whether DYRK1A acts upstream of BMPR2, for example through phosphorylation-mediated inhibition, or whether both pathways converge on shared downstream effectors, such as NFAT or EGR1. Clarifying these mechanisms may identify novel regulatory nodes and facilitate the development of therapeutic strategies targeting both DYRK1A and BMPR2 pathways.

Although the investigation of DYRK1A in other CVDs, such as atherosclerosis, may provide additional insights, it is suggested that priority should be given to resolving key PAH-specific challenges, such as optimizing DYRK1A inhibitors for PASMC and EC targeting, and clarifying DYRK1A-BMPR2 crosstalk. Such a focused approach may accelerate the translation of DYRK1A-targeted therapies into effective and safe treatments for PAH.

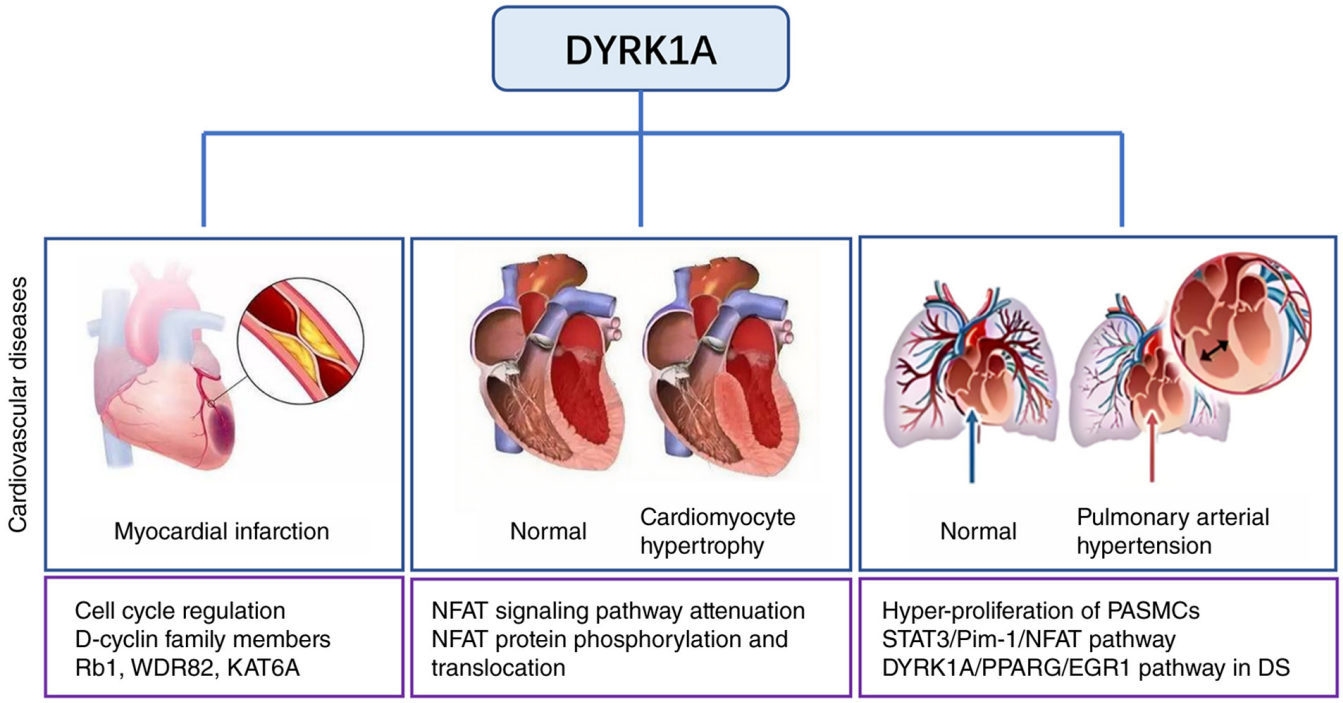

Figure 2. Regulatory effects of DYRK1A on the occurrence and development of cardiovascular diseases. DS, Down syndrome; DYRK1A, dual-specificity tyrosine phosphorylation-regulated kinase 1A; EGR1 early growth response protein 1; KAT6A, lysine acetyltransferase 6A; NFAT, nuclear factor of activated T cells; PASMCs, pulmonary artery smooth muscle cells; PPARG, peroxisome proliferator-activated receptor γ; Rb1, retinoblastoma protein 1; WDR82, WD repeat domain 82.

6. Future research directions for DYRK1A in CVD

DYRK1A has been shown to function as an important regulator in numerous CVDs, including MI, cardiomyocyte hypertrophy and PAH (Fig. 2). In particular, DYRK1A represses the cell cycle progression of cardiomyocytes and limits cardiac repair following MI by phosphorylating transcription factors involved in cell cycle regulation and interacting with D-cyclins, regulates cardiomyocyte hypertrophy by modulating NFAT signaling, and contributes to PAH by activating the STAT3/Pim-1/NFAT pathway. In addition, evidence from harmine treatment and transgenic mouse models suggest that DYRK1A is a potential therapeutic target in CVDs. However, several aspects of DYRK1A-mediated regulation remain unclear. For example, the functional role of DYRK1A appears to differ between the acute phase of MI and chronic remodeling, suggesting that stage-specific therapeutic strategies may be required. Furthermore, the crosstalk between DYRK1A and other cardiovascular regulators, including AMP-activated protein kinase (AMPK), glycogen synthase kinase 3β (GSK3β) and calcineurin, remains insufficiently characterized. Elucidating these interactions will be critical for understanding the broader regulatory network of DYRK1A in CVDs.

AMPK, a key energy-sensing kinase that regulates cardiac metabolism and stress responses, may interact with DYRK1A to coordinate cardiomyocyte cell cycle progression and metabolic adaptation during post-MI repair. However, whether these proteins directly phosphorylate one another or share downstream substrates remains unclear. Similarly, GSK3β, which regulates cardiomyocyte proliferation and hypertrophy (95), and calcineurin, an upstream activator of NFAT signaling, may functionally interact with DYRK1A to fine-tune pathological responses. Investigation of these interactions may identify synergistic regulatory targets for therapeutic intervention. In addition, the role of DYRK1A in other CVDs, including atherosclerosis and doxorubicin-induced cardiomyopathy, remains largely unexplored and merits further investigation.

As maintaining balanced DYRK1A expression is essential for physiological function, therapeutic strategies may be required to differ according to disease context. Inhibition of DYRK1A may protect cardiac function following acute MI or in PAH, whereas activation of DYRK1A may be beneficial in cardiomyocyte hypertrophy. From a translational perspective, the optimization of DYRK1A modulators represents an important research priority. Current DYRK1A inhibitors, such as harmine, have shown therapeutic potential in preclinical models of Down syndrome-associated PAH; however, off-target effects, including inhibition of DYRK1B, DYRK2 and CDK5, as well as adverse effects such as neurotoxicity and gastrointestinal disturbances, limit their clinical applicability. The development of harmine derivatives with improved selectivity for the DYRK1A ATP-binding pocket may enhance therapeutic specificity. In addition, cell-type-specific delivery systems, such as pulmonary EC-targeted nanoparticles or cardiomyocyte-specific lipid carriers, may reduce off-target exposure, particularly in diseases with cell-type-specific DYRK1A functions.

Although the regulatory role of DYRK1A has been partially elucidated in MI, PAH and cardiomyocyte hypertrophy, its functions in the broader context of CVDs remain to be fully defined. Therefore, further investigation of DYRK1A function and mechanisms in additional cardiovascular conditions is

Table I. Summary of DYRK1A in major cardiovascular diseases.

Feature	Cardiovascular disease			(Refs.)
	Myocardial infarction	Cardiomyocyte hypertrophy	Pulmonary arterial hypertension	
Affected cell type	Cardiomyocytes, cardiac fibroblasts	Cardiomyocytes	PASMCs, ECs	(44,62,82)
Upstream triggers	Myocardial ischemia/reperfusion, hypoxia, inflammation	Chronic pressure overload, Ang II/AT1R activation, catecholamine/β-AR signaling, calcineurin activation	PASMCs: Hypoxia, BMPR2 mutation; ECs: Trisomy 21, BMPR2 loss-of-function	(18,46,48,63,66,84-89,92,93)
Downstream signaling pathways	Rb/E2f cell cycle, histone modification (H3K4me3, H3K27ac) via WDR82/KAT6A, TGF-β/Smad3 fibroblast activation	Calcineurin-NFAT pro-hypertrophic signaling	PASMCs: STAT3/Pim-1/NFAT; ECs: DYRK1A/ PPARG/EGR1	(18,24,57,92,93)
Role of DYRK1A	Acute phase: Inhibition of cardiomyocyte proliferation by blocking G_1/S phase transition; repression of proliferation-promoting gene transcription via epigenetic modification; chronic phase: Regulation of cardiac fibroblast activation and extracellular matrix homeostasis to prevent excessive fibrosis	Phosphorylation of the Ser-Pro repeat-3 motif of NFAT, which promotes NFAT cytoplasmic translocation and inhibits NFAT-driven pro-hypertrophic gene transcription (inhibitory in pathological hypertrophy); partial resistance under chronic stress	PASMCs: Drives hyperproliferation and apoptosis resistance via STAT3/Pim-1/NFAT activation, promoting vascular wall thickening; ECs: Suppresses PPARG activity, upregulates EGR1, impairs EC homeostasis and accelerates endothelial dysfunction and vascular remodeling (pro-pathogenic in both cell types)	(24,59,92,93)
Therapeutic strategies	Phase-specific inhibition: In acute MI, DYRK1A should be inhibited to activate the cardiomyocyte cycle and cardiac repair; DYRK1A inhibition may reduce ischemia-reperfusion injury and infarct size; in chronic remodeling, inhibition should be avoided to prevent excessive myocardial fibrosis and ventricular stiffness	Activation/moderate upregulation: Reinforcement of DYRK1A-mediated NFAT inhibition to suppress pathological myocardial growth; DYRK1A activation may prevent progression to heart failure; development of cell-specific activators to overcome chronic stress resistance	Selective inhibition: Pan-DYRK1A inhibition to block PASMC hyperproliferation; EC-targeted DYRK1A inhibition (e.g., nanoparticle delivery) to restore PPARG/EGR1 balance; optimization of inhibitors (e.g., harmine derivatives) to reduce off-target effects; cell type-specific DYRK1A inhibition may reverse pulmonary vascular remodeling	(18,59,84,95)

Ang II, angiotensin II; AT1R, Ang II type 1 receptor; DYRK1A, dual-specificity tyrosine phosphorylation-regulated kinase 1A; ECs, endothelial cells; EGR1 early growth response protein 1; H3K4me3, histone H3 lysine 4 trimethylation; H3K27ac, histone H3 lysine 27 acetylation; KAT6A, lysine acetyltransferase 6A; NFAT, nuclear factor of activated T cells; PASMCs, pulmonary artery smooth muscle cells; PPARG, peroxisome proliferator-activated receptor γ; Rb, retinoblastoma protein; TGF-β, transforming growth factor β; WDR82, WD repeat domain 82.

warranted. To further clarify DYRK1A roles across disease stages and cell types, three specific research directions are proposed.

Single-cell transcriptomics. The application of single-cell RNA sequencing to cardiac or pulmonary tissues from CVD models, such as MI or PAH models, at different disease stages may reveal cell-type-specific changes in DYRK1A expression and its downstream targets. This approach could potentially identify rare cell populations, such as proliferating cardiomyocytes or activated PASMCs, in which DYRK1A exerts key regulatory effects, and aid the discovery of stage-specific transcriptional programs mediated by DYRK1A, including those associated with acute inflammation or chronic fibrosis in MI.

Cardiac organoid modeling. Organoid technology, which closely mimics the structure and function of *in vivo* organs,

represents an advanced *in vitro* platform for studying gene function, modeling disease progression and evaluating therapeutic candidates. Cardiac organoids can be used to support research advances in the cardiovascular field (96). Human induced pluripotent stem cell-derived cardiac organoids, which recapitulate key components of human heart tissue, including cardiomyocytes, fibroblasts and ECs, provide a physiologically relevant system for investigating DYRK1A function. These models enable the simulation of disease conditions such as hypoxic stress for PAH and ischemic injury for MI, and facilitate the evaluation of DYRK1A modulators in a human-relevant context. Such approaches may reduce reliance on animal models and overcome species-specific differences in cardiovascular biology.

Cell-type-specific knockout studies. Generation of conditional knockout mouse models, such as cardiomyocyte-specific and pulmonary SMC-specific DYRK1A knockout models, represents an important strategy for dissecting the cell-autonomous effects of DYRK1A. For example, cardiomyocyte-specific knockout models may clarify whether the DYRK1A-mediated regulation of post-MI cardiac repair occurs directly within cardiomyocytes or indirectly through other cardiac cell populations, such as fibroblasts. Similarly, pulmonary EC-specific knockout models may help confirm the pathogenic contribution of DYRK1A to Down syndrome-associated PAH.

Existing evidence suggests that DYRK1A is a potential therapeutic target in CVDs and other pathological conditions. However, translational studies investigating DYRK1A modulators remain limited. Therefore, the development of highly efficient and selective DYRK1A modulators, combined with advanced mechanistic approaches using single-cell sequencing and organoid-based models, is necessary to accelerate the clinical translation of DYRK1A-targeted therapies for CVDs.

7. Conclusions

To facilitate understanding of the context-dependent roles of DYRK1A and the corresponding therapeutic implications for different cardiovascular pathologies, a summary of cell-type-specific regulatory mechanisms, upstream triggers, downstream signaling pathways and disease-specific therapeutic strategies in MI, cardiomyocyte hypertrophy and PAH is presented in Table I (18,24,44,46,48,56,57,59,62,63-66,81, 84-89,92,93).

The present review systematically summarizes the context-dependent mechanistic roles of DYRK1A in three major CVDs. In MI, DYRK1A inhibits cardiomyocyte proliferation by suppressing cell cycle-associated signaling and through epigenetic mechanisms. In cardiomyocyte hypertrophy, DYRK1A antagonizes pro-hypertrophic NFAT signaling through the direct phosphorylation of NFAT proteins. In PAH, DYRK1A promotes pathological vascular remodeling through cell type-specific pathways, including STAT3/Pim-1/NFAT signaling in PASMCs and DYRK1A/PPARG/EGR1 signaling in pulmonary ECs.

From a clinical perspective, the therapeutic modulation of DYRK1A should be tailored to the specific disease context and stage, as no universal strategy is applicable. DYRK1A inhibition may be beneficial in acute MI by the promotion of cardiac repair, and in PAH via the reduction of vascular remodeling, particularly when combined with cell type-specific targeting. By contrast, DYRK1A activation may be advantageous in pathological cardiomyocyte hypertrophy Notably, the non-specific inhibition of DYRK1A should be avoided in chronic MI and hypertrophic conditions to prevent adverse outcomes, including myocardial fibrosis and aggravated cardiac remodeling.

Despite these advances, important gaps remain, including limited understanding of stage-specific regulatory shifts of DYRK1A during chronic CVD progression, and of the crosstalk between DYRK1A and other cardiovascular signaling pathways. Addressing these gaps and developing highly selective DYRK1A modulators will be critical for advancing the translational application of DYRK1A-targeted therapies in CVDs.

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Authors' contributions

LY was responsible for writing the original draft, and for reviewing and editing. QC was also responsible for writing the original draft. JW was responsible for conceptualization and supervision. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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