DYRK1A: A promising protein kinase target for cardiomyocyte cycling and cardiac repair through epigenetic modifications

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Due to the fact that the mammalian adult heart has a very limited regenerative capacity of the myocardium, cardiomyocyte loss cannot be corrected following myocardial injury. Sustained cardiomyocyte loss can further cause cardiac remodeling and heart failure. Although clinical therapies to stimulate cardiac regeneration was currently unavailable, increasing evidence has emerged that promoting the endogenous cardiac regeneration by inducing the proliferation of pre-existing cardiomyocytes is an effective and promising approach to treat myocardial injury and heart failure.[1,2] Some molecules and signaling pathways, e.g., Hippo-YAP, NRG1-ErbB, AKT, and GSK-3, have been reported to be potential regulators of cardiomyocyte proliferation.[3] Recently, some noncoding RNAs such as miR-15, miR-17-92 cluster, and miR-128, have been identified to regulate cardiac regeneration through cardiomyocyte proliferation, and targeting these noncoding RNAs may have protective effects to improve myocardial repair and preserve cardiac function after myocardial injury.[4] Pharmacological targeting or genetic regulation of these molecules or signaling pathways have been used to determine their functions in promoting cardiac regeneration and repair *in vivo*. Additionally, exercise is an effective way to induce physiological cardiac growth with increased proliferation markers of cardiomyocytes.[5] Exploring the molecular mechanisms and the means of intervention to enhance endogenous cardiac regeneration is very important to repair the heart after myocardial injury.

DYRK1A is a dual specificity tyrosine-regulated protein kinase expressed ubiquitously and has been reported to play important roles in regulating cell proliferation.[6] DYRK1A was previously identified as a negative regulator of cardiomyocyte cell cycle through reducing cyclin D expression and subsequent Rb phosphorylation and E2F-controled gene transcriptions that caused cell cycle arrest at G1 phase.[7] More recently, both cardiomyocyte-specific suppression and pharmacological inhibition of DYRK1A have been shown to be effective to improve cardiac function after ischemia-reperfusion injury which was closely related to enhanced cardiomyocyte cycling.[8] These observations suggest that DYRK1A can also regulate cardiomyocyte cell cycle progression, however, the underlying mechanisms remained largely unclear.

In this issue of *EBioMedicine*, Lan and colleagues elucidate the molecular mechanisms by which inhibition of DYRK1A promotes cardiomyocyte cell cycling and cardiac repair after myocardial infarction (MI) from the aspect of epigenetic modifications.[9] An increased DYRK1A expression was observed in adult mice hearts compared to that in neonatal mice hearts. DYRK1A was also higher expressed in adult mice hearts after MI. Inducible cardiomyocyte-specific ablation of DYRK1A was effective to enhance different proliferation markers in cardiomyocytes including Ki67, phospho-histone H3 (pHH3), and Aurora B (suggestive of cardiomyocyte proliferation) at 7 days post-MI *in vivo*, and also enhanced cardiomyocyte cytokinesis as measured by time-lapse live-cell imaging *in vitro*. Suppression of DYRK1A also improved cardiac function and prevented cardiac remodeling in mice after MI. Using RNA-seq combined with biological analysis, Lan and colleagues further observed that knockdown of DYRK1A in cardiomyocytes resulted in a positive transcriptional reprogramming of gene expressions involved in cardiomyocyte cell cycling, which was probably associated with histone modifications including increased expressions of trimethylated histone 3 Lys4 (H3K4me3) and acetylated histone 3

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Lys27 (H3K27ac). Direct evidence was further obtained by ChIP-seq analysis showing that knockdown of DYRK1A enhanced the deposition enrichment of H3K4me3 and H3K27ac at the promoter regions of representative genes contributing to cell cycle activation of cardiomyocytes. DYRK1A knockdown was also related to enhanced chromatin accessibility which further facilitated the transcription of genes activating cardiomyocyte proliferations. Due to the nature of DYRK1A as a protein kinase, Lan and colleagues further proved the binding and phosphorylation activities of DYRK1A on WDR82 and KAT6A which act as H3K4 methyltransferase and histone acetyltransferase, respectively. Knockdown of DYRK1A was associated with reduced phosphorylation of WDR82 and KAT6A, thus leading to increased H3K4me3 and H3K27ac expressions and their depositions at the promoter regions of cell cycle genes. Finally, the therapeutic effect of inhibition of DYRK1A was proved by treating MI mice with harmine, a competitive inhibitor of ATP binding to the kinase pocket of DYRK1A, as evidenced by enhanced proliferation markers of cardiomyocytes *in vivo*, and attenuated cardiac dysfunction and cardiac remodeling after MI. In summary, this study underpins the beneficial effect of inhibiting DYRK1A in promoting cardiomyocyte cell cycling and cardiac repair after MI and clarifies the molecular mechanisms by linking its protein kinase activity to epigenetic modifications.

In addition to MI, the potential roles and mechanisms of DYRK1A in postanal cardiac growth and cardiac regeneration of neonates remain to be further clarified.[10] Since DYRK1A is a pleotropic kinase, further work is needed to investigate whether DYRK1A regulates other functions of cardiomyocytes (e.g., promotion of cell survival and protection from apoptosis). It is also needed to examine whether DYRK1A has functional effects on other cell types in the heart. As a ubiquitously expressed protein kinase, the heart- or cardiomyocyte-targeted delivery of DYRK1A inhibitors deserves to be developed for evaluation of its efficacy and safety *in vivo*. To conclude, the current study provides a deep mechanistical insight into the important contribution of DYRK1A inhibition to cardiomyocyte cell cycle activation, and indicates that inhibition of DYRK1A is a promising target which promotes cardiomyocyte cycling and cardiac repair after MI through epigenetic modifications.

Contributors

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Declaration of interests

The authors declare no conflict of interest.

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