Heart disease is a major cause of human death worldwide. The switching/sucrose non-fermenting (SWI/SNF) complex plays a crucial role during heart development and heart disease. Brahma-related gene 1 (Brg1), a critical adenosine triphosphatase (ATP) catalytic subunit of the SWI/SNF complex, participates in several physiological and pathological processes by utilizing the energy generated by ATP hydrolysis to regulate gene transcription, DNA repair, and DNA replication. And Brg1 is involved in systemic diseases, including nervous, cardiovascular, and immune system diseases. Recently, the role of Brg1 in heart disease has been studied in-depth. Increasing evidence has implicated Brg1 in oxidative stress mechanism, apoptosis, proliferation, and cardiac remodeling during heart disease. These findings have suggested that Brg1 is involved in disease development through diverse physiological functions [Figure 1].

Brg1, which is more than 1600 amino acid residues in length, contains multiple domains. The N-terminal Glutamine-Leucine-Glutamine (QLQ) domain participates in protein-protein interactions and may be involved in determining protein conformational structure. The helicase/SANT-associated (HSA) domain is associated with helicases and DNA-binding proteins. The BRM and KIS (BRK) domain is thought to be associated with transcription and interacts with the chromodomain helicase DNA binding domain and the DEAD/DEAH cassette helicase domain (DExDc). The AT-hook motif binds to other DNA interaction domains. The bromodomain of Brg1 is involved in the identification of acetylated lysines in the H3 and H4 histone tails. All of these domains can be used to identify modified histones or to recruit Brg1 chromatin-remodeling activity.

However, how Brg1 chromatin-remodeling activity is involved in physiological and pathological effects during disease progression remains unclear. Brg1 can recruit chromatin-remodeling complexes by binding to the regulatory factor zinc finger protein, Brg1/Brm-associated factor subunits, or transcription factors via a specific DNA-binding domain. Brg1 can form transcriptional activation complexes with specific transcription factors and histone-modifying enzymes. Although Brg1 is closely associated with transcriptional activation, multi-subunit complexes with ATPase activity can combine with histone deacetylases (HDACs), histone methyltransferases, and methyl CpG binding proteins to participate in transcriptional repression and gene silencing. Therefore, Brg1 could represent a promising prognostic biomarker for the treatment of several diseases. Although the mechanism through which Brg1 regulates heart disease is not yet fully understood, the elucidation of the functions and the underlying regulatory mechanisms through which Brg1 exerts its effects are of great significance for the treatment of heart disease.

Brg1 expression can be reactivated during the pathological stimulation of the mature adult heart, triggering cardiac remodeling associated with hypertrophy. A previous study has also reported that Brg1 is upregulated in the cardiomyocytes and endothelial cells, forming a complex with forkhead box protein M1 that triggers pathological cardiac hypertrophy. Simultaneously, Brg1 can also regulate cardiac hypertrophy via the myosin heavy chain (MHC) promoter. Chang et al. reported that Brg1 could be reactivated and upregulated, forming a complex with multiple HDACs and poly (ADP-ribose) polymerase to induce the conversion of α-MHC to β-MHC, eventually resulting in cardiac hypertrophy. In contrast, the knockout of Brg1 prevented the transformation from α-MHC to β-MHC, contributing to the alleviation of cardiomyocyte hypertrophy. In addition, the knockdown of Brg1 has been shown to impair the recruitment of Brg1 and the histone H3K4 methylation complex to the endothelin 1 promoter region, which consequently improves cardiac hypertrophy. In conclusion, Brg1 is likely associated with the development of cardiac hypertrophy via various molecular pathways.

Aortic aneurysm is a chronic, degenerative cardiovascular disease. The early manifestation of aortic aneurysm is the conversion of smooth muscle cell phenotypes, and Brg1...
controls the expression of the aortic smooth muscle cell phenotype. Studies have indicated that Brg1 can be recruited to the microRNA promoter to promote chromatin remodeling, regulating the conversion of the smooth muscle cell phenotype. Brg1 mediates the maintenance, differentiation, and proliferation of aortic smooth muscle through the regulation of cell-specific gene expression in aortic aneurysms. Clinical studies have shown that patients with thoracic aortic aneurysms are characterized by the significantly increased expression of Brg1 compared with normal individuals, and Brg1 can regulate the long non-coding RNA hypoxia-inducible factor (HIF1a) antisense RNA (HIF1A-AS1) in human aortic smooth muscle cells.[11] In addition, aneurysms are associated with the massive expression of matrix metalloproteinase 2 (MMP2) and MMP9, and Brg1 can be recruited to the MMP2 promoter.[12] These findings indicated that Brg1 serves as a significant factor in the pathogenesis of aortic aneurysms.

Brg1 regulates gene transcription and might induce heart failure through the reprogramming of cardiac gene expression. The disruption of the balance between Brg1 and T-box transcription factor 5 (Tbx5), Tbx20, and NK2 homeobox 5 (NKX2–5) can lead to severe cardiac anomalies. Studies have revealed that either the overdevelopment or underdevelopment of myocardial trabeculae can cause heart failure, and Brg1 promotes the development of myocardial trabeculae by binding the disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS1) locus near the immediate promoter region, which maintains ADAMTS1 repression.[13] During heart failure, α-MHC and β-MHC undergo gene-programmatic transformations. Willis et al.[14] reported the occurrence of heart failure in Brg1/Brm-knockout mice. These findings indicate that Brg1 can mediate the molecular mechanisms that cause heart failure, which suggests that Brg1 may be a potential therapeutic target for the treatment of heart failure.

Type 2 diabetes, a common metabolic disease, has been associated with the increased risk of diabetic cardiomyopathy and atherosclerotic cardiovascular disease. Fang et al.[15] showed that Brg1 mediates inflammation-induced
endothelial injury in the pathogenesis of atherosclerosis by being recruited to the adhesion molecules (CAM) Promoters. Evidence has indicated that diabetes can impair the nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated recruitment of Brg1, which promotes Z-DNA formation and RNA polymerase II recruitment, and decreases heme-oxidase 1 (HO-1) and signal transduction and activator of transcription 3 (STAT3) induction.[15,16] These reports have indicated that Brg1 plays a special role in the pathogenesis of diabetic cardiomyopathy.

The timely and effective recovery of coronary flow can alleviate myocardial injury caused by ischemia during the treatment of coronary heart disease. However, reperfusion itself can also cause myocardial injury, which is referred to as myocardial ischemia-reperfusion injury (MIRI).[17] In the zebrafish heart, Brg1 interacted with Dnmt3ab to suppress cdkn1c by increasing the methylation of CpG sites in the cdkn1c promoter to promote heart regeneration. Studies have found that Brg1 facilitates the formation of Z-DNA and the subsequent recruitment of RNA polymerase II, which can enhance the Nrf2-mediated expression of STAT3 and HO-1 to attenuate MIRI.[18] In contrast, another study revealed that the H3K9 lysine demethylase 3A interacts with Brg1 at the NADPH oxidase (NOX) promoter to activate NOX transcription, which can result in cardiac ischemia-reperfusion injury. Brg1 deficiency may ameliorate cardiac infarction by repressing adhesion molecules, which are associated with reduced infarct size.[19] Furthermore, Zhang et al.[20] reported that the knockdown of Brg1 could block the transactivation of podocalyxin-like protein 1 by the Brg1-KDM4B complex in situ, which was shown to reduce neutrophil infiltration and cardiac ischemia-reperfusion injury. There are no doubts that the relationship between Brg1 and cardiac ischemia-reperfusion injury remains controversial, which may be related to the cell model or experimental environment. These indicated that Brg1 might be crucial for the study and treatment of MIRI, which needs further research.

In summary, Brg1 plays critical role in heart disease through transcriptional activation, transcriptional repression, and the binding of cardiac transcription-related factors. Brg1 may represent a potential target for various therapeutic strategies to address the pathogenesis, treatment, and clinical prognosis of heart disease. However, understanding the effects of Brg1 regulation during heart disease requires further basic and clinical studies.

Conflicts of interest
None.

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