Chinese Medical Journal®

Role of Brahma-related gene 1 (*Brg1*) in heart disease

Wen-Bo Huang, Wen-Yang Liu, Gui-Ling Xie

Department of Anesthesiology, Heyuan People's Hospital, Heyuan, Guangdong 517000, China.

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.[1,2] 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.[3] 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).[4,5] 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.[6] 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[7] 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*[8] 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.[9] 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*

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001480

Correspondence to: Dr. Gui-Ling Xie, Department of Anesthesiology, Heyuan People's Hospital, No.733 Wenxiang Road, Heyuan, Guangdong 517000, China
E-Mail: 0821xgl@sina.com

Chinese Medical Journal 2021;134(9)

Received: 20-10-2020 **Edited by:** Ning-Ning Wang

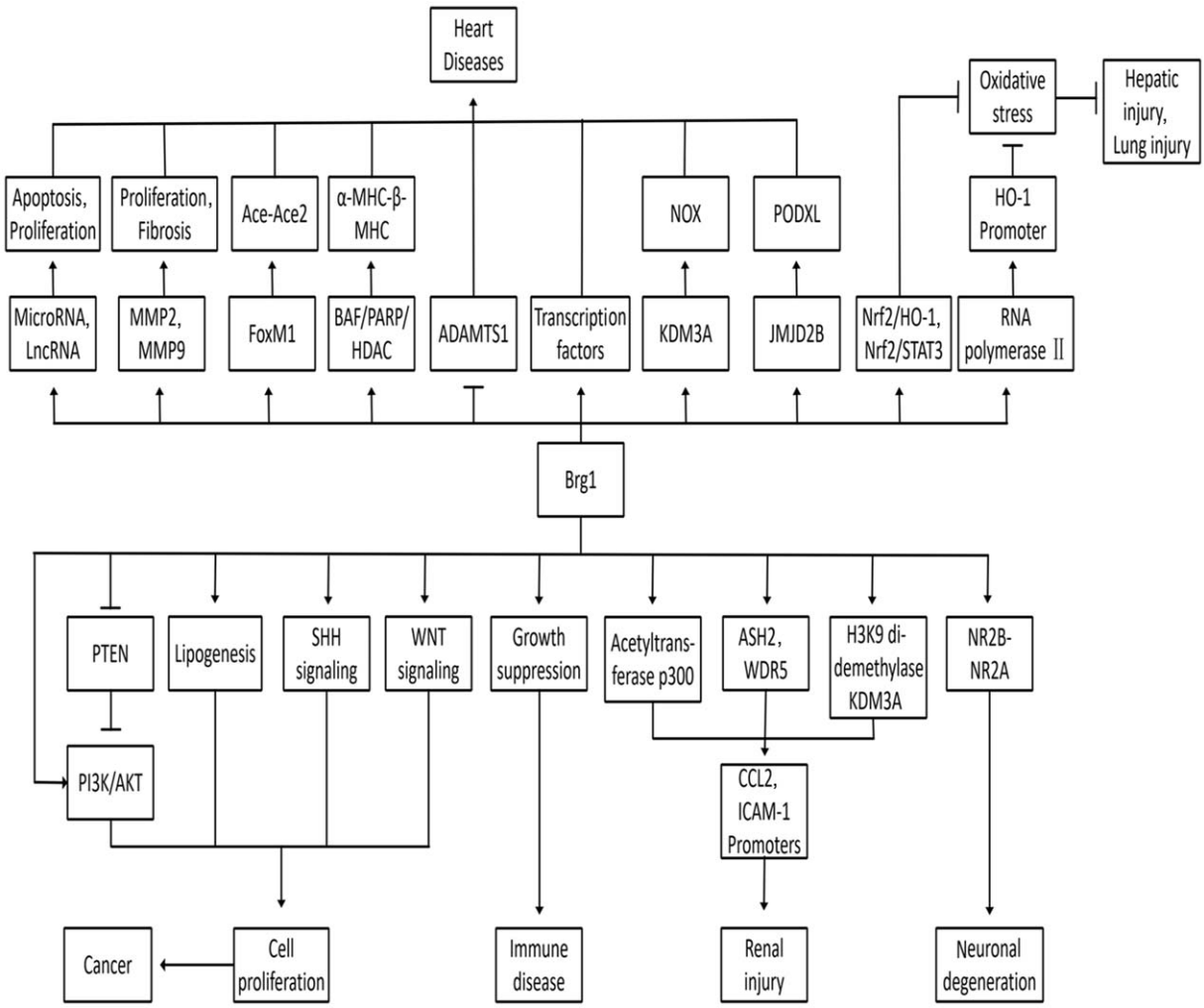

Figure 1: Physiological mechanisms underlying the association of increased *Brg1* level with diseases development. "→" indicates promoted effects and "⊣" indicates inhibited effects. Ace: Genes encoding angiotensin-converting enzymes; AKT: Protein kinase B; ASH2: A component of the mammalian histone methyltransferase complex; BAF: Brg1/Brm-associated factor; CCL2: Pro-inflammatory mediator; FoxM1: Forkhead box M1; ICAM-1: Intercellular Adhesion Molecule 1; JMJD2B: A histone H3K9 demethylase; KDM3A: H3K9 lysine demethylase 3A; NR2B-NR2A: N-methyl-D-aspartate receptor (NMDAR) subunits; PARP: Poly (ADP-ribose) polymerase; PI3K: Phosphoinositide 3-OH kinase; PODXL: Podocalyxin; PTEN: Phosphatase and tensin homolog; SHH: Sonic Hedgehog; WDR5: A component of the mammalian H3K4 methyltransferase complex; WNT: Wingless/Int-1.

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.[10] *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 aneurysm 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.[2,16] 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.

References

1. Xiao C, Gao L, Hou Y, Xu C, Chang N, Wang F, *et al*. Chromatin-remodelling factor *Brg1* regulates myocardial proliferation and regeneration in zebrafish. Nat Commun 2016;7:13787. doi: 10.1038/ncomms13787.
2. Li H, Yao W, Irwin MG, Wang T, Wang S, Zhang L, *et al*. Adiponectin ameliorates hyperglycemia-induced cardiac hypertrophy and dysfunction by concomitantly activating Nrf2 and Brg1. Free Radic Biol Med 2015;84:311–321. doi: 10.1016/j.freeradbiomed.2015.03.007.
3. Trotter KW, Fan H-Y, Ivey ML, Kingston RE, Archer TK. The HSA domain of Brg1 mediates critical interactions required for glucocorticoid receptor-dependent transcriptional activation in vivo. Mol Cell Biol 2008;28:1413–1426. doi: 10.1128/MCB.01301-07.
4. Trotter KW, King HA, Archer TK. Glucocorticoid receptor transcriptional activation via the BRG1-dependent recruitment of TOP2β and Ku70/86. Mol Cell Biol 2015;16:2799–2817. doi: 10.1128/MCB.00230-15.
5. Allen MD, Religa TL, Freund SMV, Bycroft M. Solution structure of the BRK domains from CHD7. J Mol Biol 2007;371:1135–1140. doi: 10.1016/j.jmb.2007.06.007.
6. Pal S, Yun R, Datta A, Lacomis L, Erdjument-Bromage H, Kumar J, *et al*. mSin3A/histone deacetylase 2- and PRMT5-containing Brg1 complex is involved in transcriptional repression of the Myc target gene cad. Mol Cell Biol 2003;23:7475–7487. doi: 10.1128/mcb.23.21.7475-7487.2003.
7. Yang J, Feng X, Zhou Q, Cheng W, Shang C, Han P, *et al*. Pathological Ace2-to-Ace enzyme switch in the stressed heart is transcriptionally controlled by the endothelial Brg1-FoxM1 complex. Proc Natl Acad Sci USA 2016;113:E5628–E5635. doi: 10.1073/pnas.1525078113.
8. Chang C, Han P. Epigenetic and lncRNA regulation of cardiac pathophysiology. Biochim Biophys Acta 2016;1863:1767–1771. doi: 10.1016/j.bbamcr.2016.03.005.
9. Weng X, Yu L, Liang P, Li L, Dai X, Zhou B, *et al*. A crosstalk between chromatin remodeling and histone H3K4 methyltransferase complexes in endothelial cells regulates angiotensin II-induced cardiac hypertrophy. J Mol Cell Cardiol 2015;82:48–58. doi: 10.1016/j.yjmcc.2015.02.010.
10. Zhang H, Sun Z, Yu L, Sun J. MiR-139-5p inhibits proliferation and promoted apoptosis of human airway smooth muscle cells by downregulating the Brg1 gene. Respir Physiol Neurobiol 2017;246:9–16. doi: 10.1016/j.resp.2017.07.004.
11. Wang S, Zhang X, Yuan Y, Tan M, Zhang L, Xue X, *et al*. Brg1 expression is increased in thoracic aortic aneurysms and regulates proliferation and apoptosis of vascular smooth muscle cells through the long non-coding RNA HIF1A-AS1 in vitro. Eur J Cardio-Thorac Surg 2015;47:439–446. doi: 10.1093/ejcts/ezu215.
12. Xu W, Xu H, Fang M, Wu X, Xu Y. MKL1 links epigenetic activation of MMP2 to ovarian cancer cell migration and invasion. Biochem Biophys Res Commun 2017;487:500–508. doi: 10.1016/j.bbrc.2017.04.006.
13. Hota SK, Benoit G. ATP-dependent chromatin remodeling during mammalian development. Development 2016;143:2882–2897. doi: 10.1242/dev.128892.
14. Willis MS, Holley DW, Wang Z, Chen X, Quintana M, Jensen BC, *et al*. BRG1 and BRM function antagonistically with c-MYC in adult cardiomyocytes to regulate conduction and contractility. J Mol Cell Cardiol 2017;105:99–109. doi: 10.1016/j.yjmcc.2017.02.003.
15. Fang F, Chen D, Yu L, Dai X, Yang Y, Tian W, *et al*. Proinflammatory stimuli engage Brahma related gene 1 and Brahma in endothelial injury. Circ Res 2013;113:986–996. doi: 10.1161/CIRCRESAHA.113.301296.
16. Wang Y, Li H, Huang H, Liu S, Mao X, Wang S, *et al*. Cardioprotection from emulsified isoflurane postconditioning is lost in rats with streptozotocin-induced diabetes due to the impairment of Brg1/Nrf2/STAT3 signalling. Clin Sci 2016;130:801–812. doi: 10.1042/CS20150617.
17. Liu Y, Sun C, Xue F, Yang G, Li H, Liu Q, *et al*. Effect of autophagy inhibition on the protection of ischemia preconditioning against myocardial ischemia/reperfusion injury in diabetic rats. Chin Med J 2018;131:1702–1709. doi: 10.4103/0366-6999.235867.
18. Gao S, Yang ZC, Shi RL, Xu D, Li HB, Xia ZY, *et al*. Diabetes blocks the cardioprotective effects of sevoflurane postconditioning by impairing Nrf2/Brg1/HO-1 signaling. Eur J Pharmacol 2016;779:111–121. doi: 10.1016/j.ejphar.2016.03.018.
19. Li Z, Zhang X, Liu S, Zeng S, Yu L, Yang G, *et al*. Brg1 regulates NOX gene transcription in endothelial cells and contributes to cardiac ischemia-reperfusion injury. Biochim Biophys Acta 2018;1864:3477–3486. doi: 10.1016/j.bbadis.2018.08.002.
20. Zhang X, Liu S, Weng X, Zeng S, Yu L, Guo J, *et al*. Brg1 deficiency in vascular endothelial cells blocks neutrophil recruitment and ameliorates cardiac ischemia-reperfusion injury in mice. Int J Cardiol 2018;269:250–258. doi: 10.1016/j.ijcard.2018.07.105.

How to cite this article: Huang WB, Liu WY, Xie GL. Role of Brahma-related gene 1(*Brg1*) in heart disease. Chin Med J 2021;134:1061–1063. doi: 10.1097/CM9.0000000000001480