

The role and molecular mechanism of FoxO1 in mediating cardiac hypertrophy

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Abstract

Cardiac hypertrophy can lead to heart failure and cardiovascular events and has become a research hotspot in the field of cardiovascular disease. Despite extensive and in-depth research, the pathogenesis of cardiac hypertrophy is far from being fully understood. Increasing evidence has shown that the transcription factor forkhead box protein O 1 (FoxO1) is closely related to the occurrence and development of cardiac hypertrophy. This review summarizes the current literature on the role and molecular mechanism of FoxO1 in cardiac hypertrophy. We searched the database MEDLINE via PubMed for available evidence on the effect of FoxO1 on cardiac hypertrophy. FoxO1 has many effects on multiple diseases, including cardiovascular diseases, diabetes, cancer, aging, and stem cell activity. Recent studies have shown that FoxO1 plays a critical role in the development of cardiac hypertrophy. Evidence for this relationship includes the following. (i) FoxO1 can regulate cardiac growth/protein synthesis, calcium homeostasis, cell apoptosis, and autophagy and (ii) is controlled by several upstream signalling molecules (e.g. phosphatidylinositol 3-kinase/Akt, AMP-activated protein kinase, and sirtuins) and regulates many downstream transcription proteins (e.g. ubiquitin ligases muscle RING finger 1/muscle atrophy F-box, calcineurin/nuclear factor of activated T cells, and microRNAs). In response to stress or external stimulation (e.g. low energy, oxidative stress, or growth factor signalling), FoxO1 undergoes post-translational modification and transfers from the cytoplasm to nucleus, thus regulating the expression of a series of target genes in myocardium that are involved in cardiac growth/protein synthesis, calcium homeostasis, cell apoptosis, and autophagy. (iii) Finally, targeted regulation of FoxO1 is an effective method of intervening in myocardial hypertrophy. The information reviewed here should be significant for understanding the roles of FoxO1 in cardiac hypertrophy and should contribute to the design of further studies related to FoxO1 and the hypertrophic response. It should also shed light on a potential treatment for cardiac hypertrophy.

Keywords Cardiac hypertrophy; Heart failure; Pathogenesis; FoxO1; Therapeutics

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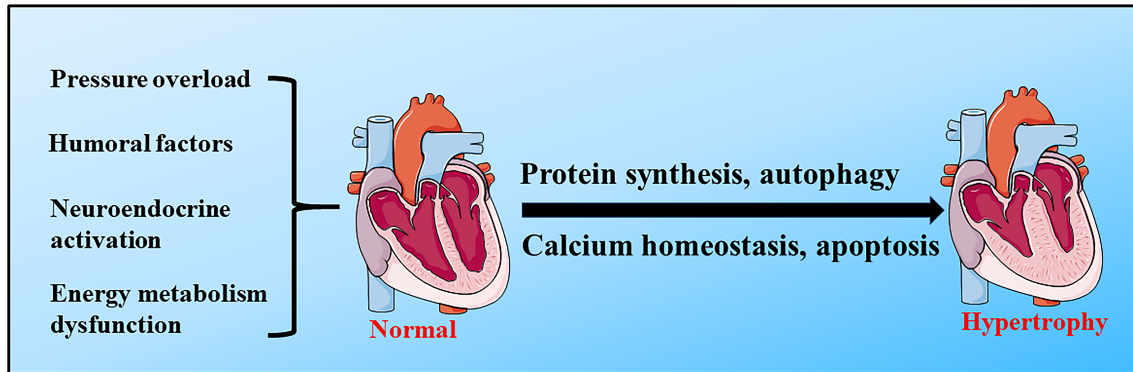
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Introduction

Cardiac hypertrophy is a common complication of cardiovascular diseases, such as hypertension, heart valve disease, myocardial infarction, and congenital heart disease.^{1,2} Cardiac hypertrophy is an adaptive response of the heart to a variety of pathological stimuli, such as increased load, changes in humoral factors, neuroendocrine activation, and energy metabolism disorders.¹ This condition has compensatory significance in the early stage and can lead to arrhythmia and

heart failure in the last stage.³ Cardiac hypertrophy develops into heart failure, one of the main causes of death.⁴ The pathogenesis of cardiac hypertrophy is complex, including cardiomyocyte hypertrophy, proliferation of fibroblasts, and interstitial fibrosis.^{1,5} Imbalance of calcium homeostasis, changes in protein synthesis, apoptosis, and autophagy are important factors affecting the occurrence, development, and outcome of cardiac hypertrophy^{6–8} (Figure 1). Many studies have shown that forkhead box protein O 1 (FoxO1) is involved in the development of cardiac hypertrophy. FoxO1

Figure 1 The pathophysiological mechanism of cardiac hypertrophy. Cardiac hypertrophy develops in the normal heart in response to a variety of pathological stimuli, such as pressure overload, changes in humoral factors, neuroendocrine activation, and energy metabolism disorders, which may be involved in the imbalance of calcium homeostasis, changes in protein synthesis, apoptosis, and autophagy.



regulates calcium homeostasis, protein synthesis, apoptosis, and autophagy in cardiomyocytes.

This review article discusses the signal transduction mechanism of FoxO1 in the pathogenesis of cardiac hypertrophy and possible new therapeutic targets for effective prevention and treatment of cardiac hypertrophy.

The FoxO family

The FoxO family, also known as forkhead proteins, has four subtypes in mammals: FoxO1 (FKHR), FoxO3 (fkhr1), FoxO4 (AFX), and FoxO6. The conserved domains shared by the four members are the nuclear localization sequence, nuclear output sequence, and C-terminal trans-active domain.⁹ In response to stress or external stimulation (e.g. low energy, oxidative stress, or growth factor signalling), FoxO proteins undergo post-translational modification (PTM) in nuclear localization sequence and nuclear output sequence domains and transfer from the cytoplasm to nucleus, thus regulating the expression of a series of genes in tissues.^{9,10}

The FoxO family plays a major role in regulating stress resistance, metabolism, cell cycle arrest, and apoptosis.¹¹ Different subtypes of FoxO proteins play different functions in different diseases. FoxO1 is the most widely studied subtype and has multiple effects on many diseases, including cardiovascular disease, diabetes, and cancer.¹² It is also an important regulator of aging and longevity.¹³ FoxO1 is controlled by several upstream signalling molecules [e.g. phosphatidylinositol 3-kinase (PI3K)/Akt, AMP-activated protein kinase (AMPK), and sirtuins] and it regulates many downstream transcription proteins [e.g. calcineurin/nuclear factor of activated T cells (NFAT), muscle RING finger 1 (MuRF1)/muscle atrophy F-box (MAFbx), pyruvate dehydrogenase kinase 4 (PDK4), and peroxisome proliferator-activated

receptor α (PPAR γ) coactivator-1 α (PGC-1 α)].¹³ Notably, FoxO1 can regulate calcium homeostasis, protein synthesis, apoptosis, and autophagy, which have been confirmed to inhibit cardiac hypertrophy in many studies^{12,14} (Figure 2).

Role and molecular mechanism of FoxO1 in cardiac hypertrophy

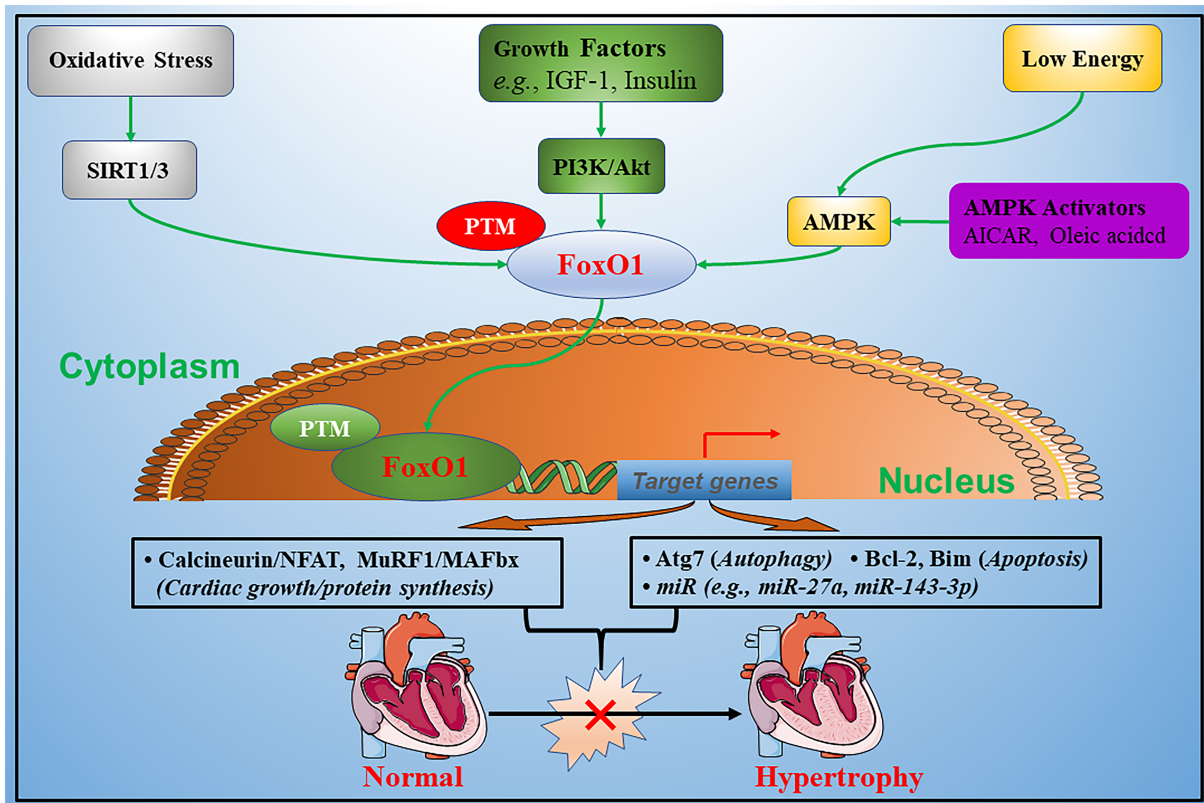
FoxO1 and cardiac growth/protein synthesis

In cardiac metabolism, insulin regulates glucose transport, glycolysis, glycogen synthesis, lipid metabolism, protein synthesis, and cardiomyocyte apoptosis. In recent years, increasing evidence has shown that insulin is an important regulator of physiological cardiac growth.¹⁵ Therefore, negative regulation of insulin signals may have a protective effect on myocardial hypertrophy. Activation of FoxO1 reduces the insulin signal by inhibiting calcineurin and protein phosphatase 2A in cardiomyocytes.^{16,17} In contrast, FoxO1 inactivation increases insulin sensitivity and promotes growth and proliferation of cardiomyocytes.¹⁸ However, FoxO1 overexpression restores FoxO activity and inhibits cardiac hypertrophy.¹⁸ The mechanism of FoxO1 inhibiting cardiac growth may be related to inhibition of the calcineurin/NFAT pathway.¹⁹ In short, FoxO1 activation inhibits growth factor-induced cardiac growth by regulating the calcineurin/NFAT pathway.

FoxO1 and apoptosis of cardiomyocytes

Progressive death of cardiomyocytes caused by apoptosis is due to pathological cardiac hypertrophy and ventricular remodelling. Ischaemia and its resulting hypoxia are well-known factors promoting apoptosis. Exposure of H9c2

Figure 2 Regulatory network of FoxO1 in cardiac hypertrophy. FoxO1 can inhibit cardiac hypertrophy by regulating many target genes, including calcineurin/NFAT, MAFbx/MuRF1, Atg7, Bcl-2, Bim, and miR. All these genes are involved in cardiac growth/protein synthesis, calcium homeostasis, cell apoptosis, and autophagy. PTM-mediated FoxO1 nuclear translocation plays a critical role in regulating the expression of target genes. In response to stress or external stimulation (e.g. low energy, oxidative stress, or growth factor signalling), FoxO1 undergoes PTM and transfer from the cytoplasm to nucleus, thus regulating the expression of a series of target genes in myocardium. AICAR, 5-aminoimidazole-4-carboxamide ribonucleoside; AMPK, AMP-activated protein kinase; Atg7, autophagy-related gene 7; FoxO1, forkhead box protein O 1; IGF-1, insulin-like growth factor 1; MAFbx, muscle atrophy F-box; miR, microRNAs; MuRF1, muscle RING finger 1; NFAT, nuclear factor of activated T cells; PI3K, phosphatidylinositol 3-kinase; PTM, post-translational modification; SIRT1/3, silencing information regulator 2-related enzyme 1/3.



cells to hypoxia for 24 h significantly increased apoptosis, and its mechanism may be closely related to the decreased expression of FoxO1 mRNA and protein.²⁰ Aging spontaneously hypertensive rats progressed from cardiac hypertrophy to fibrosis via apoptosis of cardiomyocytes at the end of hypertensive heart disease.²¹ The molecular mechanism of these pathological changes may be involved in Akt-FoxO1/Bcl-2/survivin/caspase3 signal activation.²¹ Furthermore, FoxO1 can also activate Bim expression to promote chronic intermittent hypoxia-induced apoptosis of cardiomyocytes, hypertrophy, and perivascular fibrosis.¹⁴ Consistent with the above results, a recent study indicated that increasing phosphorylation of Akt-FoxO1 can attenuate cardiomyocyte apoptosis and decrease the expression of N-terminal pro brain natriuretic peptide, a marker of heart failure.²² Therefore, FoxO1 inactivation significantly increases oxidative stress-induced cardiomyocyte apoptosis, and the molecular mechanism may be related to FoxO1 regulating apoptosis-related genes (e.g. *Bcl-2*, *Bim*).

FoxO1 and autophagy of cardiomyocytes

Autophagy is considered a type of cell self-protection, which is closely related to cardiovascular disease. Cardiac hypertrophy occurs because of mechanical load, but hypertrophy can subside during unloading. Autophagy plays a major role in regulating the regression of cardiac hypertrophy.²³ Transgenic mice with heart-specific high expression of FoxO1 have a small heart and significantly increased autophagy.²³ These results indicate that autophagy and FoxO1 play a unique role in regression of cardiac hypertrophy under mechanical load. Furthermore, overexpression of SIRT3 promotes autophagy and reduces cardiac hypertrophy, and the molecular mechanism is increased deacetylation of FoxO1.²⁴

So far, the mechanism of FoxO1 regulating autophagy in cardiomyocytes is not clear. Acetylation and Akt-induced phosphorylation may play an important role in the translocation of FoxO1 into the nucleus and the interaction with autophagy-related gene 7 (Atg7) to induce autophagy.^{9,25-}

²⁷ Moreover, oxidative stress can promote the separation of deacetylases SIRT1 or SIRT3 from the substrate FoxO1 and up-regulate the acetylation of FoxO1, which is necessary for the combination of FoxO1 and Atg7 to stimulate autophagy.^{9,27}

FoxO1 and ubiquitination

The main pathways of protein degradation in eukaryotic cells include the mitochondrial enzyme pathway, lysosomal enzyme pathway, and the most important ubiquitin proteasome system (UPS) pathway.²⁸ Ubiquitin-activating enzyme catalyzes the activation of ubiquitin molecules and binding of activated ubiquitin molecules with ubiquitin cross-linked enzyme by a high energy bond. Ubiquitin ligase then recognizes the ubiquitin cross-linked enzyme ubiquitin complex and catalyzes transfer of ubiquitin molecules to the target protein. Once the ubiquitination process is disordered, it can lead to dysfunction of the UPS, destroy the dynamic balance of protein synthesis and decomposition in cardiomyocytes, and lead to increased protein levels in cells. Therefore, ubiquitin-related enzymes and the UPS play an important role in the occurrence and development of cardiac hypertrophy.

The ubiquitin ligases MuRF1 and MAFbx (atrogin-1) degrade some important components of myofibrils, such as cardiac troponin I, myogenic determination factor, myosin, myosin light chain 2, and troponin C.²⁹ Because the ubiquitin ligases MuRF1 and MAFbx have negative effects on cell size, they are used as a marker of muscle atrophy or protein degradation.³⁰ Atrophic remodelling is mediated by the UPS, which induces muscle-specific E3 ubiquitin ligase atrogin-1/MAFbx and MuRF1 through a FoxO-dependent pathway in the early stage and then activates the autophagy–lysosomal system.³¹ A previous study showed that transgenic mice with high expression of atrogin-1 showed enhanced ubiquitination of FoxO1 and up-regulation of downstream target genes, which can reduce cardiac hypertrophy.³² Recent research showed that SIRT3 can combine with FoxO1 and activate its deacetylation.²⁴ Deacetylated FoxO1 is transferred to the nucleus to promote expression of the downstream E3 ubiquitin ligases MuRF1 and MAFbx, thus alleviating myocardial hypertrophy.²⁴ Additionally, increased cardiac weight caused by hypertrophic growth is attributed to increased insulin growth factor-1/Akt/FoxO1 signalling and down-regulation of atrogin-1/MAFbx.³³ A recent study showed that FoxO1 activity was targeted by muscle-specific atrogin-1 ubiquitin ligase, which attenuated aging-related myocardial fibrosis.³⁴ These findings suggest that FoxO1 plays an important role in the development of cardiac hypertrophy by regulating ubiquitination.

FoxO1 and the calcineurin/NFAT pathway

Calcineurin is directly regulated by calcium in the process of cell signal transmission and plays a role in dephosphorylation.

The calcineurin/NFAT pathway is widely present in cardiac muscle, skeletal muscle, and vascular smooth muscle cells. This pathway promotes the proliferation of cardiac muscle, skeletal muscle, and fibroblasts and, more importantly, participates in regulating cardiac hypertrophy and myocardial apoptosis.³⁵ FoxO proteins repress cardiac hypertrophic growth by inhibiting the calcineurin/NFAT pathway.¹⁹ Over-expression of FoxO1 in cardiomyocytes selectively enhances Akt/protein kinase B (PKB) activity, inhibits calcineurin, reduces insulin sensitivity, and inhibits cardiac hypertrophy.¹⁶ Consistent with findings of previous studies, a recent study also showed that FoxO1 activation reduced the expression of NFATc3, thus alleviating arsenic-induced cardiac hypertrophy in H9c2 cells.³⁶ In general, these findings support that FoxO1 represses cardiac hypertrophy by inhibiting the calcineurin/NFAT pathway.

FoxO1 and the PI3K/Akt pathway

PI3K plays a critical role in insulin metabolism. PKB, also known as Akt, is the main effector of the PI3K pathway. Akt can phosphorylate a variety of intracellular substrates, such as glycogen synthetase kinase-3 and FoxO proteins, regulating cell growth, metabolism, and survival.¹⁵ Continuous activation of FoxO1 enhances Akt/PKB activity and inhibits insulin signalling and cell growth.¹⁷ In mice with mutation of R2M (N488I mutation of the *Prkag2*), FoxO1 overexpression inhibits excessive cardiac growth by increasing insulin sensitivity and Akt activation.¹⁸ Additionally, increased cardiac weight caused by hypertrophic growth is attributed to increased insulin-like growth factor-1/Akt/FoxO1 signalling and down-regulation of atrogin-1/MAFbx.³³ In contrast, Akt2 ablation prevents aging of the heart, and its mechanism is mainly via restoration of FoxO1-related autophagy and mitochondrial integrity.³⁷ Cardiac hypertrophy and fibrosis developed in mice exposed to ambient particulate matter (PM_{2.5}), and the mechanism may be related to the PI3K/Akt/FoxO1 signal.³⁸ Thus, FoxO1 plays an important role in regulating myocardial hypertrophy by regulating the PI3K/Akt pathway.

FoxO1 and the AMPK pathway

AMPK is a highly conserved master regulator of metabolism, which restores energy balance during metabolic stress both at the cellular and physiological levels. Recent advancements demonstrated that AMPK protects against cardiac hypertrophy by inhibiting protein synthesis through many transcriptional regulation factors, including FoxOs, NFAT, and PPAR α .^{18,36,39} Activation of AMPK by 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR, a specific AMPK activator) attenuates hypertrophy of cardiomyocytes by regulating

FoxO1/MuRF1 signalling.³⁹ Notably, mutation of AMPK γ 2 subunit inactivated FoxO1 and stimulated proliferation and hypertrophy of cardiomyocytes.¹⁸ In contrast, overexpression of FoxO1 rescued abnormal growth of the heart.¹⁸ Recently, oleic acid was shown to activate AMPK and increase FoxO1 nuclear translocation, thus reducing NFATc3 expression and attenuating arsenic-induced cardiac hypertrophy.³⁶ These findings suggest that AMPK protects against cardiac hypertrophy by regulating the transcription factor FoxO1.

FoxO1 and sirtuins

Previous studies have reported that histone deacetylase plays a major role in regulating pathological heart growth.⁴⁰ SIRT1 and SIRT3 are members of the sirtuins family; both are class III histone deacetylases. Accumulating evidence indicates that sirtuins play critical roles in modulating many processes and pathways, including redox signalling, metabolism, and longevity.⁴¹ Mammalian sirtuins have also been linked to aging and several age-related chronic diseases including cardiovascular disease, neurodegenerative disorders, and cancer.⁴¹ Recent studies have shown that SIRT1 and SIRT3 play an important role in preventing the occurrence and development of myocardial pathological hypertrophy.^{24,42,43} In transgenic mice, moderate overexpression of SIRT1 reduces cardiac hypertrophy, apoptosis/fibrosis, and cardiac dysfunction via FoxO-dependent mechanisms.⁴² In addition, treating mice with a low-fat diet improved diastolic function, reduced myocardial hypertrophy, decreased SIRT1 expression, increased FoxO1 acetylation, and increased astrogin-1 expression as compared with a high-fat diet combined with heart failure.⁴³ Similarly, SIRT3 attenuated angiotensin II-induced myocardial hypertrophy via deacetylation of FoxO1.²⁴ In summary, these studies show that SIRT1 and SIRT3 can inhibit cardiac hypertrophy by regulating FoxO1. Therefore, FoxO1 may be an important target for treating cardiac hypertrophy.

FoxO1 and microRNAs

MicroRNAs (miR) play a critical role in regulating mRNA expression and cardiovascular disease. Recent studies have shown that a change in miR expression levels may be the pathogenesis of cardiac hypertrophy and cardiac dysfunction.^{44–47} MiR-27a knockout could induce cardiac dysfunction by activating FoxO1 in mice.⁴⁷ Furthermore, in patients with coronary heart disease, the serum level of FoxO1 was positively correlated with miR-27a level, both significantly increased.⁴⁸ Atorvastatin, a lipid-lowering drug, increased cell viability, reduced the cell surface area, and caused apoptosis in H9c2 cardiomyocytes treated with angiotensin II.⁴⁹ The molecular mechanism of atorvastatin may be related to activation of AMPK, further promotion of FoxO1

activation, and suppression of miR-143-3p level.⁴⁹ From bioinformatics analysis, many miRs have been found to regulate cardiac hypertrophy.⁴⁴ However, the regulatory targets of these miRs and the mechanism of miR-mediated action need to be further studied.

FoxO1 and cardiac fibrosis

Myocardial fibrosis is one of the typical characteristics of cardiac hypertrophy and a proposed substrate for arrhythmias and heart failure.⁵⁰ Currently, there are only sporadic, non-specialized studies concerning the role of FoxO1 in cardiac fibrosis. The study by Das *et al.* demonstrated that murine iron overload increased FoxO1 activation and myocardial fibrosis, whereas fibrosis was ameliorated by FoxO1 inactivation.⁵¹ Cardiac fibroblast differentiation and proliferation are critical processes in the development of cardiac fibrosis. FoxO1 suppresses cardiac fibroblast proliferation via up-regulation of p21, and FoxO1 activation increases fibroblast differentiation.⁵² Hence, FoxO1 could be an attractive new target for anti-fibrotic therapy, which should be verified in future studies.

Targeting FoxO1 to therapeutically modulate cardiac hypertrophy

Cardiac hypertrophy can develop into heart failure and is also considered a risk factor of sudden cardiac death. Recently, increasing evidence has shown that FoxO1 plays vital roles in cardiac hypertrophy. Targeting FoxO1 may be a new and effective intervention in the treatment of cardiac hypertrophy (Table 1). For example, decreased FoxO1 activity inhibited the expression of PGC-1 α and aggravated chronic transverse aortic constriction-induced ventricular hypertrophy and dysfunction.⁵³ Likewise, FoxO1 improved the bioenergetics of right ventricular hypertrophy and right ventricular function by inhibiting the expression of PDK4.⁵⁴ Consistent with these findings, angiotensin 1–7 (Ang 1–7) treatment improved myocardial hypertrophy and fibrosis, which may be related to an increase in SIRT1 expression and deacetylation of FoxO1 in *db/db* diabetic mice.⁵⁵ Furthermore, exogenous hydrogen sulfide (H₂S) induced FoxO1 phosphorylation, thus improving cardiac function of diabetic mice and reducing myocardial hypertrophy and fibrosis.⁵⁶ Notably, commonly used blood glucose-lowering agents, which are closely related to FoxO1, have also been shown to inhibit cardiac hypertrophy.^{57,58} Metformin had a protective effect on myocardial hypertrophy and apoptosis after myocardial infarction.⁵⁷ However, FoxO1 silencing by siRNA could eliminate the anti-apoptotic effect of metformin.⁵⁷ Similarly, dapagliflozin treatment promoted FoxO1 phosphorylation and reduced myocardial hypertrophy, myocardial interstitial and perivascular fibrosis,

Table 1 Targeting FoxO1 in treatment of cardiac hypertrophy

Target	Characteristic	Reference
PGC-1 α	Decreased FoxO1 activity can inhibit the expression of PGC-1 α	Hu <i>et al.</i> ⁵³
PKD4	FoxO1 inhibits the expression of PKD4	Piao <i>et al.</i> ⁵⁴
Ang 1–7	Increases SIRT1 expression and FoxO1 deacetylation	Mori <i>et al.</i> ⁵⁵
H ₂ S	Induces FoxO1 phosphorylation	Ye <i>et al.</i> ⁵⁶
Metformin	Represses cardiac apoptosis by inhibiting FoxO1	Loi <i>et al.</i> ⁵⁷
Dapagliflozin	Promotes FoxO1 phosphorylation	Shi <i>et al.</i> ⁵⁸

Ang 1–7, angiotensin 1–7; FoxO1, forkhead box protein O 1; H₂S, hydrogen sulfide; PKD4, pyruvate dehydrogenase kinase 4; PGC-1 α , PPAR γ coactivator-1 α .

as well as cell apoptosis in mice with transverse aortic constriction.⁵⁸ All these findings highlight the important role of FoxO1 in cardiac hypertrophy remodelling. Targeting FoxO1 is expected to be a new target for treating cardiac hypertrophy and preventing heart failure.

Conclusions

With the aging of the population and an increase in the incidence of hypertension, the resulting incidence of cardiac hypertrophy and cardiovascular events is also on the rise worldwide. Cardiac hypertrophy has become a research hotspot in the field of cardiovascular disease. Therefore, there is a particular need to examine the molecular mechanism of the pathogenesis of cardiac hypertrophy.

A large number of studies have shown that cardiac hypertrophy is closely related to multiple cellular signalling pathways related to FoxO1. FoxO1 may be a major transcription factor regulating the occurrence and development of cardiac hypertrophy, but its specific molecular mechanism and regulatory network are still unclear. Therefore, a thorough investigation of the regulatory mechanism of FoxO1 in the development of cardiac hypertrophy will help to better

understand the pathophysiological basis of cardiac hypertrophy and develop new drugs to prevent or reverse this disease.

Conflict of interest

None declared.

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Author contributions

W.Y. initiated this review and wrote the manuscript. Other authors revised the first draft and provided valuable comments. All authors read the manuscript and approved the final version.

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