Cardiac hypertrophy is an adaptive response to pressure or volume overload, mutations in sarcomeric proteins, or loss of contractile mass due to myocardial infarction and is a risk factor for heart failure. The sympathetic nervous and renin-angiotensin systems are proximal initiating stimuli for cardiac hypertrophy. Binding of ligands to functional receptors activates intracellular signaling involved in phosphorylation and calcium influx and alters nuclear gene expression in cardiomyocytes. Various studies have demonstrated that transcriptional regulation in the nucleus is important for pathological cardiac hypertrophy and heart failure development. Transcription factors such as myocyte enhancer factor 2 (MEF2), serum response factor (SRF), GATA binding protein 4 (GATA4), AP-1, neuron-repressive silencer factor (NRSF), nuclear factor of activated T cells (NFAT), and myocardin have been implicated as mediators of the fetal gene program that are associated with cardiac hypertrophy and heart failure. Among these, we have investigated the function of GATA4 and p300, a histone acetyltransferase (HAT) and a GATA4 coactivator, in the progression of cardiac hypertrophy and heart failure. In this review, we describe GATA4-mediated nuclear signaling in cardiac hypertrophy and heart failure.

GATA transcription factors are zinc finger domains containing transcription factors that bind to the specific consensus DNA sequence 5'-WGATAR-3'. Six members of the GATA family have been identified, of which GATA4, GATA5, and GATA6 are expressed in the heart. GATA4 plays essential roles in heart development and a GATA4 mutation has been reported in patients with congenital heart disease. GATA4-knockout mice have been reported to die at early embryonic stages and GATA4 transgenic mice have been reported to show significant cardiac growth. These data strongly indicate that the cardiomyocyte-specific transcription factor GATA4 regulates gene transcription associated with cardiac hypertrophy. Various reports have demonstrated that GATA4 in cardiomyocytes plays important roles in the transcription of hypertrophic genes such as α- and β-myosin heavy chain (α- and β-MHC), myosin light chain 1/3 (MLC1/3), cardiac troponin C, cardiac troponin I, atrial natriuretic factor (ANF), brain natriuretic peptide (BNP), and endothelin 1 (ET-1).

In addition to its established roles in cardiac hypertrophy, GATA4 regulates cell survival and anti-apoptotic signaling. In adult cardiac myocytes, Kakita, et al reported that the calcineurin/NFAT/GATA4 pathway is required for ET-1-mediated protection against cardiac myocyte apoptosis. Cardiac-specific deletion of GATA4 induces apoptosis by alteration of the gene expression implicated in cellular apoptosis after pressure-overload. The overexpression of GATA4 has been shown to prevent cardiac myocyte apoptosis induced by anthracyclines.
such as daunorubicin and doxorubicin. \textsuperscript{21} Additionally, GATA4 has been demonstrated to regulate the expression of Bcl-2, an anti-apoptotic protein, in cardiac myocytes, and has been shown to be involved in erythropoietin-induced cardioprotection against ischemia/reperfusion injury in the mouse heart.\textsuperscript{22,23}

Regulation of GATA4 activity by post-translational modification and protein interaction

GATA4 expression and post-translational modifications are altered in the heart during cardiac hypertrophy and heart failure. GATA4 post-transcriptional modifications are important for transcriptional activity, and GATA4 activity is reportedly regulated by modifications such as acetylation, phosphorylation, methylation, and SUMOylation (Table). Interactions between GATA4 and other proteins are also important to regulate DNA binding activity and gene transcription.

**Acetylation:** We have shown that acetylation of GATA4 by p300, a histone acetyltransferase (HAT), is essential to induce hypertrophic gene transcription, cardiomyocyte hypertrophy, and heart failure development (Figure).\textsuperscript{24,25} Transcriptional co-activator p300 was first identified as an E1A binding protein; it serves as a HAT, a scaffold protein or bridge for transcription factors and other components of the basal transcription machinery to facilitate chromatin remodeling, and it activates gene transcription. Cardiac-specific p300 transgenic mice have shown acceleration of left ventricular remodeling after myocardial infarction, but the acceleration of remodeling in HAT activity-lacking p300 transgenic mice is attenuated,\textsuperscript{24,25} indicating that the HAT activity of p300 is necessary for left ventricular remodeling after myocardial infarction. The zinc finger domain of the c-terminus of GATA4 contains some residual lysine groups and plays important roles in the capacity to bind to DNA and to other factors. We analyzed the sites of p300-induced GATA4 acetylation, and found that 4 lysine residues (K311, K318, K320, and K322) were acetylated by p300; additionally, point mutations of these residues to alanine inhibited cardiomyocyte hypertrophy as a dominant-negative mutant.\textsuperscript{26} We have identified cyclin-dependent kinase 9 (Cdk9), which is a component of positive transcription elongation factor b, as a novel GATA4 binding partner. We reported that Cdk9 promotes cardiomyocyte hypertrophy and p300/GATA4 pathway activation by phosphorylation of p300 and promotion of the HAT activity.\textsuperscript{25} The acetylation of transcription factors is also regulated by histone deacetylases. Histone deacetylase 2 (HDAC2) and a small homeodomain factor, Hopx, mediate deacetylation of GATA4.\textsuperscript{28} However, the details of regulation of GATA4 deacetylation are still unclear.

**Phosphorylation:** GATA4 activation induced by hypertrophic stimulation has been demonstrated to be associated with GATA4 phosphorylation.\textsuperscript{29,30} The mitogen-activated protein kinase (MAPK) cascade is a key biochemical signal which mediates hypertrophic responses.\textsuperscript{31} Because GATA4 with the S105A point mutation, which cannot be phosphorylated by ERK, inhibited MEK1-induced hypertrophic responses in cultured cardiomyocytes, GATA4 may function downstream from the ERK signaling pathway in hypertrophic responses.\textsuperscript{32} GATA4 is also activated through direct serine phosphorylation by the p38 MAPK pathway, which is a main branch of the MAPK cascade and mediates hypertrophic growth in cultured cardiomyocytes.\textsuperscript{33} It has been reported that the Rho/Rho kinase (ROCK) pathway is upstream of GATA4 phosphorylation by ERK and p38 MAPK. In cardiomyocytes, the Rho/ROCK pathway is involved in GATA4 phosphorylation and hypertrophic responses.\textsuperscript{34} In embryonic cardiomyocytes, CDK4 phosphorylates GATA4 and inhibits cardiomyocyte differentiation.\textsuperscript{35} On the other hand, GATA4 phosphorylation at S160 by CDK4 is required for cyclin D2-dependent cardiogenesis.\textsuperscript{36}
The nucleocytoplasmic shuttling of GATA4 is reported to be regulated by phosphorylation. Glycogen synthase kinase 3-β (GSK3-β) directly phosphorylates GATA4 and thereby decreases basal and adrenergic-stimulated GATA4 in the nucleus by activating the nuclear export system. The deletion of GSK3-β in mice induces hypertrophied cardiomyopathy through increased nuclear GATA4 expression. These results suggest that the phosphorylation of GATA4 by GSK3-β negatively regulates GATA4 transcriptional activity. Serine 261 of GATA4 is also phosphorylated by ERK, RSK, and PKA. Moreover, we demonstrated that curcumin, a p300-specific HAT inhibitor, prevents cardiomyocyte hypertrophy and increases basal and adrenergic-stimulated GATA4 in the nucleus by activating the nuclear export system.

These findings summarized in this review highlight that a new therapy targeting the transcription pathway has been developed, and we hope that the developed drug improves the quality of life and prognosis of patients with heart failure.

**References**

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