This Review is part of a thematic series on Gene Expression in Hypertrophy and Stress, which includes the following articles:

- Gene Expression in Fibroblasts and Fibrosis: Involvement in Cardiac Hypertrophy
- Roles of Cardiac Transcription Factors in Cardiac Hypertrophy
- Ras, Akt, and Mechanotransduction in the Cardiac Myocyte
- G Protein–Coupled Signaling and Gene Expression
- Genetic Models and Mechanisms of Transcription in Cardiac Hypertrophy

Ryozo Nagai, Guest Editor

Roles of Cardiac Transcription Factors in Cardiac Hypertrophy

Hiroshi Akazawa, Issei Komuro

Abstract—Different cell types, equipped with unique structure and function, synthesize different sets of proteins on the basis of different patterns of gene expression, even though their genomes are identical. Cardiac transcription factors have been reported to control a cardiac gene program and thus to play a crucial role in transcriptional regulation during embryogenesis. Recently, postnatal roles of cardiac transcription factors have been extensively investigated. Consistent with the direct transactivation of numerous cardiac genes reactivated in response to hypertrophic stimulation, cardiac transcription factors are profoundly involved in the generation of cardiac hypertrophy or in cardioprotection from cytotoxic stress in the adult heart. In this review, the regulation of a cardiac gene program by cardiac transcription factors is summarized, with an emphasis on their potential role in the generation of cardiac hypertrophy. (Circ Res. 2003;92:1079-1088.)

Key Words: cardiac transcription factors ■ gene expression ■ cardiac hypertrophy ■ cardiogenesis

Cardiomyocytes are terminally differentiated and lose their ability to proliferate soon after birth. Thereafter, cardiomyocytes grow in cell size without cell division to adapt to a demand for an increased workload. In a number of pathological conditions (eg, hypertension, valvular disease, myocardial infarction, and cardiomyopathy) that impose overwork on the heart, postnatal cardiomyocytes undergo cardiac hypertrophy. Although cardiac hypertrophy is initially compensatory for an increased workload, prolongation of this process leads to congestive heart failure, arrhythmia, and sudden death. At the cellular level, cardiac hypertrophy is characterized by an increase in cell size and protein synthesis and reactivation of the fetal gene program. In addition, recent large-scale expression analyses have identified numerous genes other than fetal genes or immediate-early genes that were upregulated in hypertrophied hearts, including genes encoding proteins involved in signaling pathways and energy metabolism. The points at issue are how extracellular hypertrophic stimulation is perceived and converted into intracellular signals and how these signals change the transcriptional program that eventually leads to cardiac hypertrophy. With regard to the differential gene expression induced by hypertrophic stimulation, it is reasonable to assume that cardiac transcription factors play the leading part, because they directly regulate a number of cardiac genes that are upregulated in hypertrophied myocardium.

Cardiac transcription factors are defined, in this context, as essential transcriptional activators that are expressed predominantly in the myocardium and that regulate the expression of the
cardiac genes encoding structural proteins or regulatory proteins characteristic of cardiomyocytes. Recent studies have established the notion that cardiac transcription factors govern the intricate process of cardiogenesis by regulating cardiac-specific gene expression. Indeed, functional analysis of the cis-regulatory elements has revealed that GATA4 directly regulates basal expression of a spectrum of cardiac-specific genes, such as α-myosin heavy chain (α-MHC), myosin light chain 1/3 (MLC1/3), cardiac troponin C, cardiac troponin I, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), cardiac-restricted ankyrin repeat protein (CARP), cardiac sodium-calcium exchanger (NCX1), cardiac m2 muscarinic acetylcholine receptor, A1 adenosine receptor, and carnitine palmitoyl transferase 1β.10,13

Besides supporting the basal transcription levels of these cardiac genes and thus conferring tissue specificity on cardiomyocytes, GATA4 is critically involved in inducible gene expression evoked by a variety of hypertrophic stimulations. For example, GATA-binding elements are required for the upregulation of β-MHC or angiotensin II type 1a receptor in response to aortic constriction.14,15 In addition, GATA-binding elements are responsible for inducible gene expression of BNP in the hearts of bilaterally nephrectomized rats.16 Furthermore, in cultured cardiomyocytes, upregulation of NCX1 or BNP by adrenergic stimulation is mediated by GATA-binding elements within the regulatory regions of the individual genes.17,18

Consistent with the essential role of GATA4 in activating the gene program in response to hypertrophic stimulation, the overexpression of GATA4 generated cardiac hypertrophy both in cultured cardiomyocytes19,20 and in the hearts of mice20 (Table 1). These results suggest that GATA4 is a sufficient transcriptional regulator for the generation of cardiac hypertrophy. Moreover, the overexpression of a dominant-negative GATA4 by adenoviral gene transfer inhibited an agonist-induced increase in protein synthesis and hypertrophic gene expression in cultured cardiomyocytes.20 Although electrical stimulation upregulates GATA4 expression,21 the expression levels of GATA4 are not affected by

### TABLE 1. Transgenic Overexpression of Wild-Types or Dominant-Negative Mutants

<table>
<thead>
<tr>
<th>Cardiac Transcription Factor</th>
<th>Effects</th>
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<tr>
<td>GATA4 Wild-type</td>
<td>Hypertrophic myocardial cell growth with hypertrophic gene expression</td>
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### TABLE 2. Expression Levels or Activities of Cardiac Transcription Factors in Hypertrophied Hearts

<table>
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<tr>
<th>Cardiac Transcription Factor</th>
<th>State</th>
<th>Stimulation</th>
<th>References</th>
</tr>
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</tr>
<tr>
<td></td>
<td></td>
<td>α-Adrenergic agonist</td>
<td>20, 23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>β-Adrenergic agonist</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ET-1</td>
<td>25, 26</td>
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<tr>
<td></td>
<td></td>
<td>Ang II</td>
<td>27</td>
</tr>
<tr>
<td>MEF2</td>
<td>Enhanced DNA binding</td>
<td>Pressure overload</td>
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</tr>
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<td></td>
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<td>Volume overload</td>
<td>70</td>
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<td>Csx/Nkx2-5</td>
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<td></td>
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<td>α-Adrenergic agonist</td>
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<td>β-Adrenergic agonist</td>
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<td>HAND</td>
<td>Downregulated expression</td>
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<td>α-Adrenergic agonist</td>
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TABLE 3. Posttranslational Modification by Kinases During Cardiac Hypertrophy

<table>
<thead>
<tr>
<th>Factor</th>
<th>State</th>
<th>Stimulation</th>
<th>References</th>
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<tbody>
<tr>
<td>GATA4</td>
<td>ERK</td>
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<tr>
<td>MEF2</td>
<td>p38 MAPK</td>
<td>Activation?</td>
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</tr>
<tr>
<td></td>
<td>ERK5</td>
<td>Activation?</td>
<td>75, 76, 78</td>
</tr>
<tr>
<td>Csx/Nkx2-5</td>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAND</td>
<td>Unknown</td>
<td></td>
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</tbody>
</table>

hypertrophic stimulation induced by pressure overload, 22 α-adrenergic agonists, 20,23,25 or endothelin-1 (ET-1). 25 On the basis of an increase in DNA-binding activity of GATA4 in response to pressure overload14,15,22 or neurohumoral stimulation by α-adrenergic agonists, 20,23 β-adrenergic agonists, 18 ET-1, 25,26 or angiotensin II27 (Table 2), it is reasonable to postulate that GATA4 is activated through posttranslational modification by hypertrophic stimulation (Table 3).

Indeed, recent studies have demonstrated that GATA4 activation induced by phenylephrine (PE) stimulation is coupled with serine phosphorylation of GATA4. 23,24 Extra-cellular signal–regulated kinase 2 (ERK2) directly phosphorylates GATA4 in vitro, and PE-induced phosphorylation and activation of GATA4 are inhibited either by incubation with an ERK kinase (MEK1) inhibitor or by adenoviral transfection of dominant-negative MEK1, indicating an essential role of the ERK pathway in GATA4 activation. The ERK pathway, one of the ternary branches of the mitogen-activated protein kinase (MAPK) cascades, is a key biochemical signal that mediates hypertrophic responses. 28,29 In this respect, GATA4 may function as a transcriptional effector acting downstream from the ERK signaling pathway activated by hypertrophic stimulation, because dominant-negative GATA4 inhibited MEK1-induced hypertrophic responses in cultured cardiomyocytes. 24 GATA4 is also activated through direct serine phosphorylation by the p38 MAPK pathway, 19,26 which is another branch of the MAPK cascades and mediates hypertrophic growth in cultured cardiomyocytes. 30–32 Pharmacological inhibition of p38 MAPK attenuated ET-1–induced protein synthesis in addition to DNA binding and phosphorylation of GATA4. 26

A recent report has suggested that Rho and ROCK, a target of RhoA, are linked to PE-induced GATA4 activation through the ERK pathway. 33 Moreover, the potentiation of GATA4 transcriptional activity through p38 MAPK is induced by RhoA, a member of the Rho family of GTPases, which regulate diverse cellular events such as transcriptional regulation, cell growth control, and membrane trafficking as well as cytoskeletal organization. 34 In cardiomyocytes, Rho is critically involved in mediating hypertrophic features 35 induced by mechanical stress 36 and G-protein–coupled receptor agonists such as PE, 37–40 angiotensin II, 41,42 and ET-1. 43 Collectively, these observations highlight the role of GATA4 as an essential transcriptional effector by which divergent protein phosphorylation pathways integrate during the generation of cardiac hypertrophy.

The transcriptional activity of GATA4 is regulated through its nucleocytoplasmic shuttling mechanism. Glycogen synthase kinase 3β (GSK3β) directly phosphorylates GATA4 and thereby decreases basal and β-adrenergic–stimulated GATA4 expression in the nucleus by activating the nuclear export system. 44 Phosphorylation of GATA4 by GSK3β negatively regulates GATA4 transcriptional activity, in con-
GATA4.54,61 SRF is a transcriptional regulator of a wide variety of cardiac-specific genes, and cardiac overexpression of SRF induces hypertrophic features in mice.65 MEF2 is another important transcription factor regulating the cardiac gene program during myocardial cell hypertrophy. Transcriptional synergy based on protein-protein interaction involving GATA4 and these transcriptional factors may be implicated in the generation of cardiac hypertrophy.

Taken together, GATA4 transcriptional activity is positively regulated by multiple signaling pathways in response to hypertrophic stimulation. GATA4 plays an essential role in transcriptional regulation during the generation of cardiac hypertrophy (Figure).

**MEF2 Transcription Factors**

MEF2 transcription factors contain a MADS (indicating MCM1, agamous, deficiens, and SRF) domain and an adjacent MEF2-specific domain in the N-terminus, which together direct dimerization and binding to their cognate DNA sequence CAT(A/T)4TAG/A.63,64 In vertebrates, 4 members (MEF2-A, MEF2-B, MEF2-C, and MEF2-D) have been identified. Although MEF2A through MEF2-D are expressed in many types of cells, their specific functions are assigned to transcriptional regulation in the immune system, neurons, and striated muscle. Especially, targeted disruption of MEF2C has been shown to lead to arrested cardiac looping and right ventricular formation during embryogenesis, and several cardiac genes have been shown to be downregulated in MEF2C-null embryos,65 indicating an essential role of MEF2 in myocardial cell differentiation. MEF2C is involved in transcriptional regulation in postnatal hearts as well, inasmuch as transgenic mice expressing a dominant-negative MEF2C have displayed attenuated postnatal growth of the myocardium67 (Table 1). Consistently, the MEF2-binding A/T-rich DNA sequences have been identified within the promoter regions of a number of cardiac genes, (eg, muscle creatine kinase gene, α-MHC, MLC1/β, MLC2v, skeletal α-actin, sarcoplasmic reticulum Ca2+-ATPase, cardiac troponin T, cardiac troponin C, cardiac troponin I, desmin, and dystrophin).63,68

In addition, MEF2 transcription factors are critically involved in the regulation of inducible gene expression during myocardial cell hypertrophy, inasmuch as the MEF2-binding site within the MLC2 promoter is required during pressure-mediated and ET-1-mediated hypertrophy.69 and MEF2 DNA-binding activity is increased in the hearts of rats subjected to pressure overload or volume overload70 (Table 2). Recent studies have elucidated complex signaling pathways that link hypertrophic stimulation and MEF2 activation (Table 3). First, MEF2 is phosphorylated by p38 MAPK,67,71–73 Specifically, p38 MAPK-MEF2 signaling is implicated in the regulation of skeletal muscle cell differentiation74 and immune response.71 Although activation of p38 MAPK induces hypertrophic growth in cultured cardiomyocytes30–32 and p38 MAPK phosphorylates MEF2 in hypertrophied heart, the pathophysiological significance of the p38 MAPK–MEF2 pathway during cardiac hypertrophy has not been fully determined. Second, MEF2 is activated through phosphorylation by ERK5, also known as big MAPK 1.75,76 The ERK5-MEF2 pathway participates in inducible gene expression of an immediate-early gene c-fos in response to growth stimulation such as serum75 or G-protein–coupled receptor agonists.77 A recent study has demonstrated that ERK5 is activated by hypertrophy-stimulating factors such as PE, leukemia inhibitory factor, and oxidative and osmotic stress in cultured cardiomyocytes.78 Additionally, dominant-negative MEK5, the MAPK kinase for ERK5, inhibited leukemia inhibitory factor–induced hypertrophic features, and transgenic overexpression of constitutively active MEK5 in the heart resulted in eccentric hypertrophy.79 Collectively, these results suggest a role of the ERK5-MEF2 pathway in the generation of cardiac hypertrophy, although it is not determined whether MEF2 is an essential downstream effector of ERK5-induced cardiac hypertrophy.

During the skeletal muscle differentiation evoked by insulin-like growth factor-1 (IGF-1), the transcriptional activity of MEF2 is activated through the phosphoinositide 3-kinase (PI3-K)–Akt pathway.79,80 Interestingly, transgenic mice overexpressing the constitutively active form of either PI3-K or Akt exhibit physiological cardiac hypertrophy characterized by proportional myocardial cell growth without interstitial fibrosis or deterioration of cardiac function.81,82 Although the transcriptional activity of MEF2 has not been examined in these transgenic mice, it may be possible that MEF2 is involved in PI3-K/Akt–mediated hypertrophic growth of cardiomyocytes.

Most important, the MEF2 factors function as important effectors that converge in the binary downstream pathway of the Ca2+ signaling. A growing body of evidence has suggested that Ca2+ signaling plays a critical role in the generation of cardiac hypertrophy.83 Increased intracellular Ca2+ binds to and activates Ca2+-binding proteins, including calmodulin (CaM), which regulates several downstream effectors, such as calcineurin and Ca2+/CaM-dependent protein kinases (CaMKs). Activation of either calcineurin54 or CaMKs64,85 induces cardiac hypertrophy both in cultured
cardiomyocytes and in murine hearts. The MEF2 activity is stimulated by CaMK, as indicated by LacZ expression in the hearts of double transgenic animals harboring activated CaMKIV and a MEF2-dependent LacZ reporter. Although CaMKs directly phosphorylate MEF2 in vitro, the activation of MEF2 by CaMK is mediated mainly through the phosphorylation of transcriptional repressors, the histone deacetylases (HDACs). Especially, class II HDACs (HDAC-4, HDAC-5, HDAC-7, and HDAC-9) associate with MEF2 to repress MEF2-induced gene expression.

In general, transcriptional activity is controlled by the state of histone acetylation, the balance of which is maintained through opposing activities of HDACs and HATs. HDACs repress gene expression through intrinsic deacetylase activity and recruitment of a transcriptional corepressor COOH-terminal–binding protein. Recent studies have demonstrated that phosphorylation of HDACs by CaMKs results in the recruitment of intracellular chaperones 14-3-3 to dissociate the HDAC-MEF2 formation. Consequently, HDACs are sequestered in the cytoplasm by the nucleocytoplasmic shuttling mechanism and MEF2 is released from HDACs in the nucleus and transcriptionally activated through binding to coactivators harboring intrinsic HAT activity, such as p300 and CBP. HDAC4 has a CaM-binding domain that overlaps the MEF2-binding domain, and dissociation of MEF2 from HDACs is also regulated by CaM, indicating that the HDAC-MEF2 complex is controlled by a series of mediators in the Ca²⁺ signaling pathway.

The implication of class II HDACs during cardiac hypertrophy is underscored by a recent report demonstrating that HDAC9-deficient mice display spontaneous cardiac hypertrophy and are predisposed to more severe hypertrophic growth after banding of the thoracic aorta. In cultured cardiomyocytes, overexpression of class II HDACs with mutations of 2 conserved CaMK phosphorylation sites blocks hypertrophic features, including agonist-induced gene expression of ANP and β-MHC and histone acetylation of the promoter regions of these genes. These data indicate the repressive role of class II HDACs in the generation of cardiac hypertrophy. Although the HDAC kinase activity is enhanced in cardiac extracts from hypertrophied hearts of mice and although CaMKs are capable of phosphorylating HDACs, it remains unclear whether CaMKs are the functional HDAC kinases. CaMKs are capable of phosphorylating HDACs, it remains unclear whether CaMKs are the functional HDAC kinases.

Recent reports have demonstrated that a novel cardiac helicase, CHAMP, is activated by MEF2 protein and acts as a suppressor of cardiac hypertrophy. CHAMP was originally identified by differential array analysis as a cardiac-specific gene downregulated in MEF2C-deficient embryos. Overexpression of CHAMP in cultured cardiomyocytes impairs PE- and serum-induced hypertrophic gene expression. These data appear contradictory to the notion that the MEF2 factors are important in regulation of hypertrophic gene expression. However, CHAMP expression is downregulated in the hearts of transgenic mice overexpressing activated calcineurin. On the basis of the enhanced activity of MEF2 in these mice, it is plausible that CHAMP expression is not dependent on MEF2 in the postnatal heart.

Collectively, MEF2 activity is enhanced in response to hypertrophic stimulation, and MEF2 functions as an essential effector of divergent intracellular signaling pathways mediating hypertrophic features (Figure).

Cardiac Homeobox Transcription Factor Csx/Nkx2-5
Csx/Nkx2-5 is a homeodomain-containing transcriptional activator, originally identified as a potential homologue of Drosophila tinman. The homeodomain of Csx/Nkx2-5 has a helix-turn-helix motif that binds to the specific consensus DNA sequence T(C/T)AAGTG. Targeted disruption of Csx/Nkx2-5 in mice caused embryonic lethality due to the arrested looping morphogenesis of the heart tube and growth retardation. The expression of several cardiac genes in the heart of Csx/Nkx2-5–deficient embryos (including MLC2v, ANP, BNP, CARP, MEF2-C, eHAND/HAND1, N-myc, Iroquois homeobox gene 4, and HOP) was reduced. In addition, direct downstream targets for Csx/Nkx2-5 (such as ANP, cardiac α-actin, A1 adenosine receptor, calreticulin, connexin40, and NCX1) have been identified. These results indicate a functional role of Csx/Nkx2-5 in the transcriptional regulation of a cardiac gene program.

In contrast to the essential role of Csx/Nkx2-5 during embryogenesis, its functional role in the postnatal heart has not been fully determined. Csx/Nkx2-5 is expressed in the adult heart and notably, its expression is upregulated in hypertrophied hearts (Table 2). Banding of the feline pulmonary artery induces right ventricular hypertrophy with increased expression of Csx/Nkx2-5 and its downstream target genes, ANP and cardiac α-actin. In PE- or isoproterenol-mediated hypertrophic hearts, expression of Csx/Nkx2-5 is stimulated as well as the expression of fetal genes, such as ANP and β-MHC, and immediate-early genes.
such as c-fos, c-jun, and Egr-1. The upregulation of Csx/Nkx2-5 expression in pressure overload–induced and agonist-induced hypertrophic hearts indicates a potential role of Csx/Nkx2-5 in the process of cardiac hypertrophy in general.

However, transgenic mice overexpressing Csx/Nkx2-5 under the control of the cytomegalovirus enhancer/chicken β-actin promoter exhibit normal-sized hearts (Table 1). The expression levels of cardiac genes such as ANP, BNP, CARP, and MLC2v are upregulated in the hearts of Csx/Nkx2-5 transgenic mice. These gain-of-function studies suggest that Csx/Nkx2-5 is not sufficient for the generation of cardiac hypertrophy but that Csx/Nkx2-5 functions to control cardiac gene program in adult hearts as well as in embryonic hearts. Csx/Nkx2-5 interacts with other cardiac transcription factors. Transcriptional activity of Csx/Nkx2-5 is modulated through physical interaction with other transcription factors such as GATA4,50 through physical interaction with other transcription factors allow fine-tuned gene expression. One of the downstream target genes identified was ANP, BNP, and eHAND/HAND1.157 We have identified several factors that interact with Csx/Nkx2-5 and modulate Csx/Nkx2-5–induced gene expression. One of the coactivating factors potentiates Csx/Nkx2-5–induced promoter activation in response to a signal evoked by hypertrophic stimulation (authors’ unpublished data, 2003). Therefore, combinatorial regulation involving Csx/Nkx2-5 and its coactivators might be necessary for the generation of cardiac hypertrophy, although it is still speculative.

A novel muscle–specific gene, Chisel (Csl), was identified by a differential screening as a target gene downregulated in Csx/Nkx2-5–null embryonic hearts.136 Overexpression of Csl in C2C12 myoblasts induced lamellipodia formation and differentiation into large myosacs in the presence of IGF-1 as a result of enhanced cell fusion. Interestingly, Csl augmented transcriptional activities of MEF2 and NFAT in an IGF-1 signaling-dependent manner. Both MEF2 and NFAT are important in the differentiation and hypertrophy of cardiac muscle as well as skeletal muscle. Although the activation of NFAT by Csl in the presence of IGF-1 is not dependent on the calcineurin pathway, it is intriguing that the downstream target of Csx/Nkx2-5 might operate in connection with the NFAT and MEF-2 transcription factors, which are involved in the generation of cardiac hypertrophy.

Recently, transgenic mice overexpressing dominant-negative mutant of Csx/Nkx2-5 under control of α-MHC promoter have been generated (Table 1). These mice show impaired cardiac function with the degeneration of cardiomyocytes. Furthermore, in response to doxorubicin, dominant-negative Csx/Nkx2-5 transgenic mice show more severe cardiac dysfunction accompanied by a larger number of apoptotic myocardial cells, although doxorubicin-induced myocardial damage is mild in transgenic mice overexpressing the wild-type of Csx/Nkx2-5. These results indicate a cardioprotective role of Csx/Nkx2-5 in postnatal hearts.

Taken together, Csx/Nkx2-5 is upregulated in response to hypertrophic stimulation and may have implications in the transcriptional regulation of the cardiac gene program in hypertrophied hearts (Figure). In the adult heart, Csx/Nkx2-5 also plays an important role in protecting the myocardium against cytotoxic damage.

HAND Transcription Factors
dHAND/HAND2 and eHAND/HAND1 are basic helix-loop-helix transcription factors that have distinctive roles in cardiac and extraembryonic development.140 The expression of eHAND is predominant in the left ventricle and is excluded from the right ventricle. Analysis of eHAND-null mice defined an essential role of eHAND in myocardial differentiation of the left ventricle.141–143 In contrast, the expression of dHAND is restricted to the right ventricle, and development of the right ventricle has been shown to be selectively compromised in dHAND-null embryos.144

Initial insight into postnatal HAND function was provided by a report showing that the expression of dHAND and eHAND is detectable in human adult hearts and that the cardiac expression of eHAND is significantly downregulated in patients with cardiomyopathies.145 Likewise, in a PE-induced hypertrophic mouse model, a chamber-specific downregulation of eHAND in the left ventricle and dHAND in the right ventricle was observed (Table 2). In addition, in abdominal aorta–banded rats, the expression of dHAND and of eHAND was shown to be downregulated in both the ventricles. The reduced expression of HAND genes may indicate a role in the inhibition of myocardial cell growth. At present, a limited number of direct downstream target genes of the HAND transcription factors have been identified. Through binding to p300, dHAND interacts with GATA4 to induce synergistic transactivation of the promoters of ANP, BNP, and α-MHC.55 Similarly, eHAND interacts with Csx/Nkx2-5 to synergistically transactivate the ANP promoter.157 Elucidation of the molecular basis of the HAND transcription factors will be required to understand the postnatal roles relevant to their reduced expression in hypertrophied hearts.

Future Issues
Functional roles of the cardiac transcription factors during cardiogenesis have been considerably deciphered. Many downstream target genes are identified, and transcriptional regulatory mechanisms whereby protein–protein interactions with other cardiac transcription factors allow fine-tuned gene expression have been clarified. Recent studies have demonstrated that GATA4 and MEF2 are involved in reactivation of the fetal gene program in response to a variety of hypertrophic stimulation and that these factors function as important effectors during the generation of cardiac hypertrophy. Furthermore, mechanistic insights have been provided into the signaling pathways that enhance the transcriptional activities of these transcription factors. In contrast to GATA4 and MEF2, Csx/Nkx2-5 participates in the activation of the hypertrophic gene program but does not have the ability to induce hypertrophic myocardial cell growth. In this respect, a challenging problem (ie, how the cardiac transcription factors influence an increase in protein synthesis and myocardial cell size) remains unsolved. An increased capacity of protein synthesis underlying hypertrophic growth is facilitated not by increased translational efficiency but by ribosome accumulation resulting from increased transcription of ribosomal DNA by the nucleolar factor UBF.147,148 Interestingly, adenoviral introduction of UBF antisense RNA into cultured cardiomyocytes abolished an increase in general protein synthesis and
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hypertrophic cell growth in response to α-adrenergic and contraction stimulation but had little effect on fetal gene expression.\(^\text{148}\) It has not been clarified whether the UBF activity is influenced by cardiac transcription factors. Comprehensive analyses of target genes regulated by cardiac transcription factors during cardiac hypertrophy will provide a clue toward solving this problem.

Transcriptional regulation by multiple cardiac transcription factors such as GATA4, MEF2, and Csx/Nkx2.5 is interrelated. It is conceivable that combinations of the ubiquitous and tissue-specific transcription factors execute regulatory decisions under a spectrum of hypertrophic conditions as well as during embryogenesis. Although transcriptional synergy has been reported to be significant in controlling the expression of several cardiac genes, an important issue (ie, how much the cooperative transcriptional regulation weighs with the generation and progression of cardiac hypertrophy) remains unsolved. It is also undetermined how the mutual interaction is regulated in response to hypertrophic stimulation. Functional analysis of the individual cardiac transcription factors and clarification of their interactive roles will be required.

Finally, whether the cardiac transcription factors may be potential therapeutic targets in cardiovascular diseases is a challenging problem. Although compensatory cardiac hypertrophy is beneficial in some pathological conditions, evidence-based studies have suggested that the regression of cardiac hypertrophy in patients leads to better prognosis.\(^\text{2}\) It is an ideal adaptation to excessive workload to enhance myocardial contractility without a pathological increase in left ventricular mass, which may be feasible, as exemplified by a rat model of \(^\text{NO}\) -nitro- \(l\) -arginine methyl ester–induced hypertension.\(^\text{149}\) Cardiac transcription factors are the potential candidates, because it is now clear that they orchestrate inducible gene expression in postnatal cardiomyocytes. Further investigation will be required to understand the molecular basis of the gene expression program directing cardiac hypertrophy and to target this for therapeutic purposes.

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