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Re-employment of developmental transcription factors in adult heart disease

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Abstract

A finite number of transcription factors constitute a combinatorial code that orchestrates cardiac development and the specification and differentiation of myocytes. Many, if not all of these same transcription factors are re-employed in the adult heart in response to disease stimuli that promote hypertrophic enlargement and/or dilated cardiomyopathy, as part of the so called "fetal gene program". This review will discuss the transcription factors that regulate the hypertrophic growth response of the adult heart, with a special emphasis on those regulators that participate in cardiac development.

Keywords

Cardiac hypertrophy; transcription factors; cardiomyopathy; gene expression; signaling; chromatin

1. Introduction

Development of the embryonic heart involves early specification of cardiac myocytes from uncommitted mesodermal progenitors, their differentiation and ability to contract and function in synchrony, and their integrated growth and proliferation as the organ becomes morphologically mature. The past decade of genetic-based approaches in the mouse has uncovered a select group of transcriptional regulators that directly program these various aspects of cardiac cell lineage commitment and/or heart morphogenesis. Transcriptional regulators such as myocyte enhancer factor 2 (MEF2), GATA4, nuclear factor of activated T cells (NFAT), serum response factor (SRF), Nkx2.5, nuclear factor κB (NFκB), Hand1/2, Smad transcription factors, and chromatin remodeling factors participate in a combinatorial code that regulates differentiation-specific gene expression and growth of the developing myocardium [reviewed in [1]]. Interestingly, many of these transcription factors are re-employed in the adult heart in response to disease states, where they are thought to mediate the re-expression of the "fetal program" and genes involved in growth. In most cases, these transcription factors are activated by signal transduction pathways initiated by membrane bound receptors in response to neural-humoral agonists. Here we will review data implicating a select group of cardiac expressed transcription factors in controlling the hypertrophic growth of the adult myocardium or its transition to dilated cardiomyopathy.

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Adult heart disease can arise from either congenital abnormalities associated with a defect in one or more cardiac developmental process, or due to acquired disorders such as longstanding hypertension, ischemia/myocardial infarction associated with coronary artery disease, valvular insufficiency, myocarditis due to an infectious agent, essential hypertrophic and dilated cardiomyopathies, and diabetic cardiomyopathy [2,3]. The majority of these disease predisposing stimuli first induce a phase of cardiac hypertrophy in which individual myocytes grow without proliferation as a means of augmenting cardiac pump function and decreasing ventricular wall tension [4,5]. However, long-term myocardial hypertrophy predisposes to heart failure, arrhythmia, and sudden death [5].

The heart senses many of the disease-inducing stimuli listed above either directly through biomechanical stretch sensitive receptors or indirectly through an array of membrane bound G protein-coupled receptors and receptors with intracellular tyrosine kinase domains that bind hormones, cytokines, chemokines, and peptide growth factors in the circulation or the extracellular milieu of the heart [6–8]. These initiating stimuli converge on a finite array of intracellular signal transduction pathways to mediate the cardiac growth/disease response. Many of the transcription factors that will be discussed here receive activating signals through phosphorylation and dephosphorylation events mediated by mitogen-activated protein kinase (MAPK), calcineurin, and insulin-like growth factor-I (IGF-I)-phosphatidylinositol 3-kinase (PI3K)-Akt, as well as through kinase-regulated shuttling of class II histone deacetylases (HDACs) [6–9]. While some of these signaling relationships that alter transcription factor activity were described in cultured neonatal rat primary cardiomyocytes, this review will focus on recent studies in genetically modified mouse models that provide additional understanding of the complexities surrounding the cardiac growth response and the transition to heart failure.

2. GATA4

Six GATA transcription factors have been identified in vertebrates and parsed into two subclasses based on their expression patterns. GATA-1, -2, and -3 are prominently expressed in hematopoietic cell lineages while GATA-4, -5, and -6 are expressed in various mesoderm and endoderm derived tissues such as heart, liver, lung, gonad, and gut [10]. GATA factors contain a highly conserved DNA binding domain consisting of two zinc fingers that direct binding to the nucleotide sequence element (A/T)GATA(A/G), as well as a potent transcriptional activation domain and domains that mediate interaction with transcriptional co-factors [10]. One of these family members, GATA4, has been extensively characterized as an essential regulator of cardiac development and differentiation, as well as in regulating survival and hypertrophic growth of the adult heart [10,11].

Traditional germline disruption of *Gata4* in the entire mouse resulted in early embryonic lethality between embryonic (E) day 7.0 and 9.5 due to defects in endoderm and ventral morphogenesis, although these embryos still generated cardiac tissue that expressed heart-specific structural genes [12,13]. To gain further insight into the role that GATA4 plays in heart development tetraploid embryo complementation was employed using *Gata4−/−* embryonic stem cells, which generated embryos that progressed further in development and showed hypoplastic ventricles and a loss of the proepicardium, resulting in lethality [14]. *Gata4* was also deleted specifically in the heart using a Cre-loxP-based approach and a *Nkx2.5-Cre* knock-in allele, which showed embryonic lethality and hypoplastic ventricles [15,16]. More recently, a heterozygous mutation in *Gata4* was associated with congenital abnormalities in cardiac septation in humans, further supporting the developmental importance of this factor [17]. Collectively, these studies underscore the importance of GATA4 in regulating development and differentiated gene expression in the heart.

GATA4 is also expressed in the adult heart where it is thought to function as a key transcriptional regulator of numerous cardiac genes including atrial natriuretic factor (ANF), b-type natriuretic peptide (BNP), α-myosin heavy chain (α-MHC), β-myosin heavy chain (β-MHC), and many others [10,11]. A direct transcriptional regulatory role for GATA4 is further supported by the observation that anti-sense GATA4 mRNA expression inhibited the basal expression of certain cardiac-expressed genes in cardiomyocyte cultures [18]. In addition to its hypothesized role in maintaining differentiated gene expression in the post-natal/adult heart, GATA4 also mediates inducible gene expression in response to hypertrophic stimuli, including pressure overload, isoproterenol, phenylephrine, and endothelin-1 [19–22]. For example, overexpression of GATA4 in culture by adenoviral gene transfer induced cardiomyocyte hypertrophy indicating the sufficiency of GATA4 in this process [22]. More significantly, expression of dominant negative GATA4 (engrailed fusion) or antisense GATA4 mRNA each blocked GATA4-directed transcriptional responses and features of cardiomyocyte hypertrophy induced by phenylephrine and endothelin-1 in culture [22,23]. *In vivo*, mild overexpression of GATA4 in the mouse heart by transgenesis induced a progressive hypertrophic response (Table 1) [22].

More recently, GATA4's necessity in mediating cardiac hypertrophy *in vivo* was demonstrated using a conditionally targeted *Gata4-loxP* allele in conjunction with two different heart-specific Cre-expressing transgenic lines that reduced GATA4 expression by 70 or 95% within myocytes. Both approaches generated mice that were viable into young adulthood, although as these mice aged they eventually developed cardiac dilation and heart failure associated with myocyte apoptosis [16]. Indeed, germline heterozygous targeted *Gata4* mice showed greater apoptosis in the heart following doxorubicin treatment [24]. With respect to cardiac hypertrophy, mice with conditional deletion of *Gata4* in the heart showed attenuated growth following 2 or 4 weeks of pressure overload or following exercise stimulation [16]. However, loss of *Gata4* did not affect post-natal growth of the heart, also referred to as developmental hypertrophy, suggesting that GATA4 function in the adult heart is specialized to regulate adaptive and maladaptive growth.

A number of stimuli that induce cardiac hypertrophy and/or heart failure are known to enhance GATA4 transcriptional activity through phosphorylation. For example, pressure overload, isoproterenol, phenylephrine, endothelin-1, angiotensin II and phorbol esters each induced phosphorylation of GATA4 resulting in enhanced DNA binding and/or transactivating activity [19,21,25–29]. We have observed that agonist stimulation of cultured cardiomyocytes or hearts results in phosphorylation of GATA4 at serine 105 through the direct action of extracellular signal-regulated kinase 1/2 (ERK1/2) and p38 MAPK [23,26]. Phosphorylation of serine 105 in GATA4 enhanced DNA binding activity and transcriptional potency, while mutation of serine 105 to alanine attenuated activity [26]. Since both ERK1/2 and p38 MAPK receive input from diverse upstream signaling pathways it suggests that serine 105 in GATA4 can serve as a key convergence point in regulating the cardiac hypertrophic response. GATA4 is also subject to negative regulation by glycogen synthase kinase 3β (GSK3β)-mediated phosphorylation, which reduced both basal and isoproterenol-induced nuclear expression of GATA4 and suppress transcriptional activity [27]. Interestingly, while overexpression of GATA6 also induced cardiac hypertrophy in cultured cardiac myocytes, GATA6 mRNA and protein are not regulated by hypertrophic signals, suggesting that GATA4 may be more highly specialized for controlling this process compared with GATA6 [22,26]. In conclusion, these various reports underscore the hypothesis that GATA4 functions as a transcriptional convergence point in the adult heart whereby multiple stress-signals alter its function as a means of modifying the cardiac hypertrophic response or the survival of individual myocytes.

3. NFAT

The calcium/calmodulin-activated protein phosphatase calcineurin (PP2B) and its downstream transcriptional effector NFAT have been implicated as critical transducers of the cardiac hypertrophic response. In response to elevated intracellular calcium, calcineurin becomes activated in the cytoplasm where it binds to NFAT and directly dephosphorylates the N-terminal regulatory domains, exposing a nuclear localization signal permitting its translocation to the nucleus and interaction with GATA4 as a means of inducing hypertrophic gene expression [30]. There are four calcineurin-regulated NFAT transcription factors, NFATc1-c4, each of which is expressed in the myocardium and exclusively localized to the cytoplasm in the unstimulated state [30,31]. Once translocated to the nucleus, NFAT family members bind a loose consensus site consisting of (G/A)GAAA, either alone or as part of an associated site that also binds AP-1 or GATA4 [30,31]. NFATc1-c4 are members of the extended cRel/NFκB super family that bind DNA through a Rel homology domain. The N-terminus of NFATc1-c4 contains a domain with multiple serine/threonine residues that is subject to phosphorylation by a diverse group of signaling kinases, resulting in cytoplasmic sequestration and inhibition of NFAT. Thus, similar to GATA4, NFAT factors function as a signaling convergence point whereby multiple stress/mitogen-activated pathways modulate transcriptional activity.

NFAT factors are important regulators of cardiac and vascular development [32]. For example, loss of *Nfatc1* in gene-targeted mice results in defective cardiac valve formation and fetal lethality [33,34]. By comparison, embryos lacking *Nfatc2/c3/c4* (triple nulls) showed defective endocardial cushion development, reduced cells in the atrioventricular canal, and thinned myocardium [35]. Double null embryos lacking *Nfatc3/c4* showed defects in vessel formation throughout the embryo [36], as well as selective defects in cardiac development characterized by thinning of the myocardium, reduced myocyte proliferation, and metabolic dysfunction [37]. Consistent with these data, expression of a dominant negative NFAT mutant in the heart using conditional transgenesis resulted in thinning of the atria and reduced expression of cardiac structural genes [38]. Thus, NFAT factors are critical regulators of several aspects of cardiac development and myocyte maturation.

Consistent with their role in regulating myocyte maturation during development, NFATs are also important regulators of myocyte growth in the adult heart. For example, cardiac overexpression of the constitutively-active calcineurin catalytic subunit or a constitutively nuclear NFATc4 mutant protein each induced massive cardiac hypertrophy that quickly transitioned to heart failure [39]. After this initial description in 1998, a series of papers emerged that essentially solidified the centrality of calcineurin as a necessary mediator of pathologic cardiac hypertrophy [30]. However, it was not immediately clear if NFATs were the critical downstream mediators of calcineurin-dependent cardiac hypertrophy, despite the fact that NFATc1–c4 are only activated by calcineurin, and the amount and timing of nuclear translocation are directly proportional to the degree of calcineurin activation *in vivo* [31]. To explore this question we generated and characterized transgenic mice containing an NFAT-dependent luciferase reporter, which showed specific induction in the heart by activated calcineurin, and repression by the calcineurin inhibitor cyclosporine [40]. Using these reporter mice, calcineurin-NFAT signaling was shown to be constitutively upregulated throughout a time course of pressure overload hypertrophy, as well as in the failing mouse heart following myocardial infarction [40]. Thus, NFAT activity is regulated during the cardiac hypertrophic response.

To directly examine the necessity of NFATs as hypertrophic mediators both dominant-negative inhibitory strategies and gene-targeted mice have been analyzed. For example, while targeted disruption of *NFATc4* did not diminish the magnitude of calcineurin transgene-dependent

hypertrophy or pressure overload hypertrophy, *NFATc3* null mice showed a significant and long-standing reduction in calcineurin-induced hypertrophy at multiple time points up to ten weeks of age. *NFATc3* gene-targeted mice were also compromised in their ability to mount an efficient hypertrophic response following aortic banding or angiotensin II infusion [41]. These results establish NFATc3 as a critical downstream mediator of calcineurin-regulated hypertrophy in the adult heart. Similarly, overexpression of a dominant negative NFAT mutant in cultured cardiomyocytes also antagonized agonist- or activated calcineurin-induced hypertrophy [42], while infusion of a cell permeable NFAT inhibitory peptide reduced pressure overload hypertrophy in rats [43]. These reports are supported by the observations that cardiac myocyte hypertrophic growth is reduced by overexpression of GSK3ß in cultured cardiomyocytes and in the hearts of transgenic mice [44–46]. GSK3ß was previously shown to directly phosphorylate the N-terminal regulatory domain of NFATc1, thus antagonizing the action of calcineurin and inhibiting nuclear shuttling of NFAT [47]. Analogous to the function of GSK3β as an NFAT kinase (inhibitor), p38 MAPK and c-Jun N-terminal kinase activity also regulated cardiac hypertrophy through an NFAT-dependent mechanism [48,49], further supporting the centrality of NFATs as integrators of the cardiac hypertrophic response by coordinating input from multiple upstream signaling pathways.

4. NFκB

Nuclear Factor *κ*B (NF*κ*B) is a transcription factor that can regulate the expression of immediate early and stress-response genes in diverse cell types. Five mammalian members of the NF*κ*B/Rel family have been cloned: NF*κ*B1 (p50 and its precursor p105), NF*κ*B2 (p52 and its precursor p100), c-Rel, RelA (p65), and RelB [50,51]. NFκB is regulated by a cytoplasmic inhibitory protein known as IκB, which is phosphorylated by IκB kinase-α (IKKα) and/or β leading to the ubiquitination and degradation of IκB, permitting NFκB nuclear translocation [51]. Upstream, IKK activity is regulated by NF-κB-inducing kinase (NIK), which itself is stimulated by a complex that is located within the tumor necrosis factor-α (TNFα) receptor.

While very little is known regarding a role for NFκB in regulating cardiac development or cardiac differentiation-specific gene expression, a fair amount is understood of its role in mediating adult myocardial disease responses. For example, NF*κ*B is involved in cardiac inflammation associated with myocarditis or sepsis, such that blockade of endotoxin- and burn trauma-induced NF*κ*B activation through I*κ*B overexpression prevented cardiac dysfunction [52,53]. Consistent with these observations, repression of NF*κ*B signaling rescues cardiac function and improves survival in a transgenic model of cardiac inflammation due to TNFα overexpression [54]. Cardiac protection observed in these models has been largely attributed to an anti-apoptosis effect, an interpretation that is consistent with some studies showing decreased myocyte death following ischemia-reperfusion injury in transgenic mice with inhibited NFκB [55].

NF*κ*B has also been implicated as a necessary and sufficient regulator of cardiac hypertrophy. For example, inhibition of NFκB in cultured cardiomyocytes by expressing select dominant-negative mutants reduced cardiac hypertrophy induced by reactive oxygen species, TNFα, myotrophin, phenylephrine, endothelin-1, and angiotensin II [56–59]. The potential importance of NFκB as a hypertrophic mediator in the adult heart was also recently demonstrated. Gene-targeted mice lacking p50 protein showed reduced heart growth in response to chronic angiotensin II infusion [60]. Moreover, transgenic mice that express a NFκB “super-repressor” mutant showed attenuated hypertrophy following angiotensin II or isoproterenol infusion [61]. This same super-repressor mutant also attenuated hypertrophy in aortic-banded rats after adenoviral-mediated gene transfer [62]. Thus, NFκB is an important central regulator of cardiac hypertrophy, although the downstream transcriptional targets underlying this growth effect remains to be elucidated.

5. MEF2

MEF2 was first identified as a muscle-enriched DNA binding activity from differentiated myotubes [63]. MEF2 DNA binding activity consists of homo- and heterodimers of four separate gene products in vertebrates, referred to as *Mef2a-d* [64,65]. MEF2 dimers bind to the consensus sequence $CTA(A/T)_4TAG$ present in the 5' transcriptional regulatory regions of most skeletal and cardiac muscle structural genes characterized to date [64,65]. In general, *Mef2a-d* genes are widely expressed in the adult vertebrate organism, although a number of specific regulatory functions have been identified in immune, skeletal muscle, cardiac muscle, and neuronal cells [66–69]. MEF2 factors are related to another MADS-box containing transcription factor known as SRF (SRF will be discussed separately) [70]. Similar to SRF, members of the MEF2 family have been implicated in regulating inducible gene expression in response to mitogen and/or stress stimulation.

The MEF2 family of transcription factors also function as essential regulators of cardiac development. For example, targeted disruption of *Mef2c* in the mouse led to early embryonic lethality associated with a cardiac looping defect, a general absence of the right ventricle, and downregulation of a subset of cardiac-specific genes [69,71]. Loss of *Mef2a* by gene targeting in the mouse led to myofiber disorganization at the cellular level coupled with right ventricular dilation at the organ level. A majority of *Mef2a* null mice die between postnatal day 2 and 10, possibly due to the disruption in cyto-skeleton architecture and/or conduction system defects [72]. The small portion of *Mef2a* null mice that survive into adulthood show a mitochondrial deficiency and possible conduction system defects [72]. While *Mef2a* and *Mef2c* nullizygous mutations presented with a cardiovascular phenotype, final examination of MEF2's function in determining the cardiac cell lineage or its differentiation may be impossible given that all 4 MEF2 family members are expressed in the early heart and each would have to be inactivated simultaneously. However, to partially address the issue of redundancy, transgenic mice were generated that expressed a dominant-negative MEF2 mutant in the heart, which resulted in early postnatal lethality associated with cardiomyocyte hypoplasia, ventricular wall thinning, and chamber dilation [73]. Collectively, these various lines of evidence suggest that MEF2 function is likely required for the proper differentiation and postnatal development of the heart.

Many lines of evidence have also implicated MEF2 as an important regulator of hypertrophic growth of the adult heart. For example, MEF2 DNA-binding activity is enhanced by pressure and volume overload-induced cardiac hypertrophy [74,75]. Similarly, stretching of neonatal cardiomyocytes in culture also increased MEF2 DNA-binding activity [76,77]. However, it was not until recently that the ability of MEF2 to promote cardiac hypertrophy *in vivo* was directly examined. Mild overexpression of MEF2A or MEF2C in the hearts of transgenic mice (α-MHC promoter) induced ventricular chamber dilation and contractile dysfunction, and predisposed the heart to greater hypertrophic growth following pressure overload stimulation. However, isolated adult cardiomyocytes from MEF2A transgenic mice showed a predominant increase in length as opposed to an increase in cross-sectional area, suggesting a phenotype of cardiac dilation and addition of sarcomeres in series, suggesting that MEF2 overexpression did not primarily drive "classic" hypertrophy [78]. Indeed, adenoviral-mediated overexpression of MEF2A or MEF2C (or MEF2VP16) in cultured neonatal cardiomyocytes induced sarcomere degeneration and focal elongation, further suggesting that MEF2 primarily promotes cardiac dilation [78]. In conclusion, data from overexpression approaches indicate that MEF2 does not directly program the adult hypertrophic growth program, but instead appears to regulate cardiac dilation and the addition of sarcomeres in series.

A number of lines of indirect evidence further implicate MEF2 as an important regulator of adult heart disease, and possibly the pathologic hypertrophic response. As will be discussed in a subsequent section, class II HDACs are important regulators of gene expression that function

in coordination with MEF2 in the regulation of muscle gene expression [79–82]. Indeed, disruption of the genes encoding *Hdac9* or *Hdac5* predispose mice to pathological hypertrophy [83,84]. One mechanism whereby MEF2 is regulated through class II HDACs involves calcium/calmodulin-dependent protein kinase (CaMK) [79,85–87]. CaMK activation leads to direct phosphorylation of select class II HDACs, facilitating their nuclear extrusion and permitting MEF2 to activate muscle- or hypertrophic-specific gene expression [79,85]. In support of this mechanism, overexpression of either CaMKIV or CaMKIIδ in the heart by transgenesis produced a phenotype of hypertrophic cardiomyopathy, while genetic inhibition of CaMKII reduced hypertrophy and improved cardiac function during infusion of isoproterenol [88–90]. MEF2 was suggested to be a primary mediator of both class II HDAC- and CaMK-dependent cardiac growth through the use of a MEF2-dependent reporter transgene in the mouse. Use of this reporter suggested that MEF2 directly responded to activated calcineurin, CaMK, and loss of *Hdac9* in the heart, all conditions that promote cardiac hypertrophy [84,88]. However, these results rely on the specificity of the MEF2-dependent reporter, which harbors concatomers of an AT-rich element from the *desmin* regulatory region placed upstream of a minimal heat shock promoter [91]. Unexpectedly, the same sequence was shown to bind another transcription factor, transcription enhancer factor 1 (TEF1) [92], which shows a similar expression pattern as MEF2 in the mouse embryo and becomes activated upon hypertrophic stimulation [92–95]. Thus, while an intriguing hypothesis, it remains to be determined if MEF2 functions as a primary downstream effector of class II HDAC- and CaMK-dependent cardiac hypertrophy *in vivo*.

MEF2 factors are also activated by cardiac hypertrophic signaling effectors such as calcineurin [96–99] and big-MAPK-1 (BMK1) [100,101]. For example, MEF2 is directly phosphorylated by BMK1, which is downstream of and activated by MEK5 [100,101]. Expression of activated MEK5 induced elongation of cardiac myocytes in culture, while activated MEK5 transgenic mice showed addition of sarcomeres in series with a loss in myocyte cross-sectional area [102]. Activated MEK5 transgenic mice also showed profound ventricular dilation, reduced fractional shortening, and activation of hypertrophic gene expression. This overall phenotype is remarkably similar to MEF2A/C transgenic mice and adMEF2A/C infected neonatal myocytes, suggesting that the MEK5-BMK1 stress-activated signaling pathway may function, in part, through MEF2 [100,101]. The conclusion that calcineurin functions upstream of MEF2 in striated muscle is another interesting hypothesis, although genetic intercrosses between MEF2A/C transgenic mice with activated calcineurin transgenic mice did not reveal enhanced cardiac hypertrophy or greater functional decompensation, suggesting an independent function of each effector [78]. In conclusion, MEF2 is likely to function as an important modulator of the cardiac disease response, especially dilated cardiomyopathy, but is probably not a direct inducer of adult hypertrophy per se.

6. SRF

SRF was first identified as a transcriptional regulator that associated with the serum response element (SRE) in the *c-fos* gene promoter to confer serum inducibility [103]. SRF is the founding member of a diverse family of proteins that dimerize to bind DNA through a MADs box domain, similar to MEF2 discussed above [70,104]. SRF binds to the consensus site CC $(AT)_6$GG, also known as CArG box, which is found in the promoters of numerous skeletal, cardiac, and smooth muscle expressed genes, as well as immediate-early response genes [70, 105]. SRF mRNA is first detected in vertebrate embryos in cardiac, smooth, and skeletal muscle lineages prior to neurulation, yet becomes more ubiquitously expressed thereafter [106,107]. *Srf* deficient mouse embryos show impaired gastrulation and lethality before mesoderm formation, preventing elucidation of SRF function as a potential regulator of muscle lineage specification or differentiation [108]. Subsequent studies with cardiac conditional gene-targeted mice demonstrated that SRF was required for the proper embryonic development of

the heart by regulating differentiation-specific gene expression involved in sarcomerogenesis and cell survival [109,110]. Interestingly, tissue-specific deletion of *Srf* in skeletal muscle resulted in perinatal lethality associated with severe tissue hypoplasia [111], collectively suggesting that SRF is critical for regulating striated muscle-specific gene expression during development.

Recent evidence has also emerged implicating SRF as a regulator of the hypertrophic growth response in the adult heart. For example, cardiac-specific overexpression of SRF in transgenic mice induced cardiac hypertrophy with collagen deposition [112]. In contrast, expression of a SRF mutant protein in the heart caused severe postnatal chamber dilation, wall thinning and premature death, suggesting a role in developmental hypertrophy [113]. Similarly, deletion of *Srf* in the adult heart using a tamoxifen-inducible cardiac-specific Cre strategy promoted progressive heart failure with reduced contractility [114]. At the cellular level, deletion of *Srf* specifically in cardiomyocytes led to disorganization in the contractile apparatus, stress fiber formation, and mislocalization and attenuated expression of sarcomeric proteins [114, 115]. Indeed, mRNA array analysis of *Srf* null cardiomyocytes revealed downregulation of genes encoding sarcomeric proteins and other cardiac transcription factors [115]. Hence, SRF expression is necessary for maintaining the basal “trophic” state of the heart, and likely for inducing heart growth in response to stimulation. Consistent with this interpretation, SRF activity was shown to be inhibited in the failing adult heart, which is typically characterized by a loss of myocyte vigor [116,117].

SRF is a highly interactive transcription factor that associates with other known hypertrophic regulatory factors that influence cellular growth. For example, SRF interacts with SMAD1/3, Nkx2–5, and GATA4 to synergistically activate muscle gene expression [118–124]. All three of these factors are discussed in different sections of this review as likely regulators of the cardiac growth response. Myocardin, a SAP domain-containing nuclear factor, was also recently identified as an important and highly potent SRF interacting partner in muscle [125, 126]. Myocardin-related transcription factors (MRTF) A and B have also been shown to interact with SRF and stimulate transcriptional activity similar to myocardin [127]. Interestingly, myocardin expression is induced in cardiac hypertrophy, and its overexpression in neonatal rat cardiomyocytes induces hypertrophy whereas a dominant-negative mutant of myocardin blocks agonist-induced growth [128]. Lastly, SRF activity is also regulated by Hop, a homeodomain-only protein that directly binds SRF where it functions as a repressor by recruiting HDACs, thereby influencing cardiac growth and/or cellular proliferation [129–131]. Taken together, SRF likely serves as a “platform’ for integrating the activity of multiple co-factors in ultimately regulating or fine-tuning the transcriptional program for postnatal and adult hypertrophic growth, as well as remodeling of the heart.

7. Smads

Smad transcription factors primarily function as inducible regulators of transforming growth factor-β (TGF-β) superfamily member signals. Ligands within the TGF-β family induce assembly of type I and type II receptors on the plasma membrane, which activate the type I receptor causing direct phosphorylation of Smad proteins in the cytoplasm, leading to their nuclear accumulation [132,133]. Smad transcription factors are divided into three subfamilies based on their structure and function: (1) Receptor-Smads (R-Smad), which includes Smad1, 2, 3, 5 and 8, (2) Cofactor-Smad (Co-Smad), which includes Smad4 that associates with R-Smads to facilitate transcriptional activation, and (3) Inhibitory-Smads (I-Smad), which includes Smad6 and 7 that inhibit activation of R-Smad/Co-Smad at multiple levels [132, 133]. In general, Smad2/3 are direct substrates of TGF-β through the TGF-β and activin receptors (TβRI and ActRIB), while Smad1/5/8 are effectors of bone morphogenic protein (BMP) and related ligands through the ALK receptors [132,133].

Smad activation downstream of TGF-β/activin/BMPs (and related ligands) regulate transcription during nearly all stages of vertebrate development, including the specification, differentiation and morphogenesis of diverse tissues [134]. During cardiac development, Smads have been shown to regulate endocardial cushion formation, valve morphogenesis and outflow tract formation downstream of TGF-β and BMP [135,136]. BMPs are also important inducers of the cardiac cell lineage, consistent with its role in inducing expression of the transcription factor Nkx2–5 [137]. For example, cardiomyocyte differentiation in P19CL6 embryonic "stem-like" cells was mediated by Smad1/4 [138]. Gene targeting of *Smad6* in mice revealed several abnormalities in the heart including hyperplasia of cells in the endocardial cushions and valves, as well as outflow tract septation defects [139]. Finally, Smad proteins were further implicated in regulating the cardiac cell lineage by the observation that GATA4 and Smad proteins regulate expression of the Nkx2–5 cardiac enhancer *in vivo* [140]

In the adult, Smad proteins are critically involved in multiple aspects of pathophysiology, including the regulation of cardiac fibrosis. Elevated expression of TGF-β and Smad2, 3 and 4 in the heart was reported after myocardial infarction and in response to cardiomyopathy [141–146]. Phosphorylation of Smad2 in cardiac fibroblasts was associated with fibrosis and scar formation, an observation that is consistent with the ability of Smad7 (I-Smad) to inhibit collagen synthesis in the same cells when overexpressed [142,146,147]. Moreover, reduction in TGF-β levels and Smad2 activity correlated with decreased fibrosis after angiotensin II receptor stimulation [142]. Finally, repression of TGF-β activity through decoy receptor over-expression, or loss of one *Tgf-β1* allele (heterozygous mice), decreased interstitial fibrosis after myocardial infarction and aging associated fibrosis, respectively [148,149]. Collectively, TGF-β-Smad activity positively regulates cardiac fibrosis, which is a major contributing factor in adult heart disease and functional impairment.

In addition to the fibrotic effects associated with TGF-β-Smad signaling in the heart, recent studies have suggested that Smad proteins can directly regulate the development of cardiomyocyte hypertrophy and progression to heart failure. Indeed, *Smad4* deficient mice developed basal cardiac hypertrophy that progressed to heart failure, manifested by contractile dysfunction, adverse remodeling and death [150]. These results suggest that Smad activation normally serves an anti-hypertropic regulatory function in the adult heart. In support of this hypothesis, the TGF-β family member growth-differentiation factor 15 (GDF-15) was shown to also function as an anti-hypertrophic regulatory factor in the adult heart in association with Smad2/3 activation [151]. Indeed, overexpression of Smad2 antagonized agonist-induced cardiomyocyte hypertrophy in culture [151]. While these results support an anti-hypertrophic role for Smad activation in cardiac myocytes, TGF-β itself is thought to be a pro-hypertrophic cytokine in the heart. For example, deletion of *Tgf-β1* in the mouse reduced angiotensin II-induced hypertrophy, although the dependency of Smads as transducers of this effect was not analyzed [152]. Transgenic mice overexpressing TGF-β1 also showed cardiac hypertrophy, supporting a prohypertrophic role, but once again, this effect was not correlated with Smad activation and may likely occur through Smad independent pathways [153]. Independent of Smad proteins, TGF-β can also elicit signals through the MAPK cascade that includes TGF-β activated kinase 1 (TAK1). Interestingly, TAK1 transgenic mice show cardiac hypertrophy [154]. Thus, diverse members of the TGF-β superfamily elicit different signaling responses in the adult myocardium, although activation of Smad proteins downstream of specific ligands appears to function in an anti-hypertrophic capacity.

8. Nkx2–5

The homeobox transcription factor Nkx2–5 (also known as Csx), which binds the DNA consensus sites 5′-TNAAGTG-3′ and 5′-TTAATT-3′, is a critical regulator of cardiac gene expression and heart development [155,156]. Nkx2–5 is highly expressed in early heart

progenitor cells as they commit to the cardiac lineage during embryogenesis, where it continues to be expressed in the heart throughout adulthood [155–158]. Three independent *Nkx2–5*-deficient mouse models were generated that showed a phenotype of uniform lethality between E9–10 associated with arrested heart tube looping morphogenesis and growth retardation [159–161]. While *Nkx2–5*-deficient embryos contained committed and differentiated cardiomyocytes, the expression of several prominent cardiac structural and transcriptional regulatory genes was downregulated [130,159,160,162–164]. Nkx2–5 expression is also critical for the proper development of the conduction system, as heterozygous gene-targeted mice or mice with a heart-specific deletion showed prominent defects [165,166]. Indeed, humans with mutations in *Nkx2–5* have congenital abnormalities characterized by aberrant ventricular septation and atrioventricular node and conduction anomalies [167].

In contrast to the well-established role that Nkx2–5 plays during embryogenesis, its functional role in the postnatal and adult heart is only partially understood. Nkx2–5 has been hypothesized to participate in the cardiac hypertrophic response given the observation that its expression is upregulated during pressure overload or stress stimulation. For example, banding of the pulmonary artery in a feline model of right-ventricular pressure overload, or phenylephrine- and isoproterenol-mediated hypertrophic growth each upregulated Nkx2–5 expression [168, 169]. In contrast to these associative data, transgenic mice overexpressing Nkx2–5 under the control of the cytomegalovirus enhancer/chicken β-actin promoter (which expresses in the heart, among other tissues) exhibited normal-sized hearts, despite increased expression of hypertrophic marker genes [170]. The simplest interpretation of these data is that Nkx2–5 can regulate a subset of hypertrophic marker and differentiation-specific genes in the heart, but such selective regulation is not sufficient to induce bona fide hypertrophic growth. Despite this conclusion, Nkx2–5 could still function as a modulator of the cardiac hypertrophic response through its known ability to interact with other cardiac transcription factors such as GATA4 [120,171–173] and SRF [119]. Indeed, Nkx2–5 interacts with the newly identified cofactor calmodulin binding transactivator (CAMTA), which itself promotes cardiomyocyte hypertrophy and activates ANF gene expression [174]. Collectively, these various reports support the hypothesis that Nkx2–5 is a critical regulator of cardiac-specific gene expression, although it may only function as a modulator of the adult cardiac hypertrophic response.

Evidence has also emerged that Nkx2–5 can function as a survival factor in the heart. For example, expression of a dominant-negative human Nkx2–5 mutant in the heart under the control of α-MHC promoter, induced cardiac dysfunction and degeneration [175]. Furthermore, injection of doxorubicin promoted more severe cardiac dysfunction and increased cardiomyocyte apoptosis in the presence of the dominant negative Nkx2–5-encoding transgene compared with control mice, suggesting that Nkx2–5 expression is cardioprotective [175]. However, the putative cardioprotective function of Nkx2–5 was disputed by the observation that simple overexpression of wildtype murine Nkx2–5 in the heart (α-MHC promoter) led to organ failure by 4 months of age with conduction abnormalities, suggesting that too much Nkx2–5 could also be of detriment [176]. Hence, too much or too little Nkx2–5 activity is detrimental to the proper function of the heart, especially for establishing and maintaining integrity of the conduction system, although likely for mechanistically distinct reasons.

9. Additional Transcriptional Regulators: Hand/Egr-1/CREB

Hand2 (dHAND) and Hand1 (eHAND) are basic helix-loop-helix transcription factors that bind E-box DNA sequence elements (5′-CANNTG-3′) and have important roles in cardiac and extraembryonic development [177,178]. The expression of Hand1 is predominantly expressed in the left ventricle and is excluded from the right ventricle. Analysis of *Hand1*-null mice defined an essential role in regulating myocardial differentiation of the left ventricle [179–181]. In contrast, the expression of Hand2 is restricted to the right ventricle, and development

of the right ventricle is selectively compromised in *Hand2*-null embryos [182]. With respect to the adult heart, very little direct evidence exists to implicate a role for Hand1 or Hand2 in acquired pathological conditions. Correlative evidence has shown that Hand1, but not Hand2, is downregulated in cardiomyopathic hearts from human patients [183]. Likewise, phenylephrine-induced hypertrophy in the mouse resulted in a chamber-specific downregulation of Hand1 and Hand2 [184]. However, in a rat model of pressure overload, Hand2 was reported to be upregulated in the right ventricle [185]. Thus, changes in myocardial Hand activity may regulate/modulate adult heart disease responses, although direct experimental evidence is needed to support or refute this possibility.

Early growth response-1 (Egr-1) is a Cys2-His2 zinc finger domain-containing transcription factor that was identified as an immediate early response gene [186]. Depending on the tissue or cell type, Egr-1 can function in a growth inhibitory [187,188] or promoting capacity [189]. Egr-1 can bind either a GC-rich element (TGCGGGGGCG) that overlaps with the binding site for Sp1, or an element comprised of the sequence TCCTCCTCCTCC. These sequence elements are present in more than 30 genes including angiotensin I converting enzyme, TNF-α, α-MHC, and Egr-1 itself [190]. Egr-1 expression is highest in brain and heart tissue, and Egr-1 overexpression can promote differentiation of P19 embryonic “stem-like” cells to the cardiac and neuronal lineages *in vitro* [191]. With respect to the adult heart, Egr-1 has been reported to regulate cardiac hypertrophy. Indeed, *Egr-1−/−* mice showed reduced cardiac hypertrophy to isoproterenol and phenylephrine stimulation [192]. This result is supported by the observation that NGF1-A binding protein 1 (Nab1) overexpressing transgenic mice showed inhibited pathologic cardiac hypertrophy, where NGF1-A functions by directly inhibiting Egr-1 [193]. Thus, Egr-1 functions as an important transcriptional mediator of cardiac hypertrophy, adding yet another inducible factor to the array of adult cardiac growth regulators.

cAMP-response element (CRE) binding protein (CREB) is a 43 kDa basic leucine zipper (bZip) transcription factor that binds to the consensus sequence of TGANNTCA in association with other members of the CREB/ATF and AP-1 family [194–198]. CREB plays a critical role in regulating gene expression in response to a variety of extracellular signals [199,200]. For example, phosphorylation of CREB on Ser133 facilitates its interaction with the CREB-binding protein (CBP), which in turn activates transcription [201–203]. CREB phosphorylation and activation can be mediated by a variety of intracellular signaling pathways including protein kinase A [204], calmodulin-dependent kinase [205], cyclic GMP signaling [206], and ribosomal S6 kinase 2 in response to activation of Ras [207]. Previous studies have suggested that CREB might be an important regulator of cardiac gene expression. The Ser133-phosphorylated and transcriptionally active form of CREB is present in chicken [208], rat [209], and human cardiomyocytes [210]. Recent studies have also suggested that the transcriptional activity of CREB is important for myogenesis [211] and cardiomyocyte gene regulation [212]. With respect to cardiac hypertrophy, expression of a dominant-negative CREB mutant in the heart induced a severe dilated cardiomyopathy, suggesting a phenotype of impaired cardiac hypertrophy [212]. Consistent with this interpretation, overexpression of the related family member, CREM, in the hearts of transgenic mice directly induced cardiac hypertrophy [213]. Thus, CREB and/or related family members may also function as important signal-responsive transcriptional regulators of adult cardiac disease states.

10. Chromatin regulation: Acetylases and HDACs

Chromatin describes the packaging of DNA in eukaryotic cells whereby nucleosomes are generated in a phased array consisting of 146 bp of DNA wrapped around an octamer of four core histones, (H3/H4 tetramer and two H2A/H2B dimers), which in turn can be assembled into a more compact configuration to limit DNA access to transcription factors, thus altering gene expression [214]. Typically, inactive genetic loci are tightly compacted in histone arrays,

whereas actively transcribed regions are loosely associated with histones in an unphased array, a process that is directly regulated by postranslational modification of histone proteins [215]. Acetylation is probably the best characterized of these modifications and is catalyzed by histone acetyl transferases (HATs), which tends to favor a loose chromatin configuration and enhanced transcriptional activity [214,215]. In contrast, HDACs promote the condensation of chromatin and the inactivation of transcription. Mechanistically, HDACs and HATs are indirectly tethered to DNA promotor sites in target genes through transcription factor interactions. The HATs that have been extensively studied with respect to cardiac gene expression regulation are p300 and CBP (CREB binding protein), which bind and confer activation potential upon multiple cardiac-expressed transcription factors [9,216]. HDACs are divided into three subclasses, although class I or II have been the most extensively characterized in mammalian cells. Class I HDACs (HDAC1, 2, 3 and 8) consist primarily of a catalytic domain, are ubiquitously expressed and found almost exclusively in the nucleus. Class II HDACs (HDAC4, 5, 6, 7, 9, 10) are expressed in a more tissue specific manner and can be exported from the nucleus upon phosphorylation by signal responsive HDAC kinases [215,217].

With respect to cardiac development, loss of the HAT p300 was associated with early embryonic lethality and defective heart development with reduced structural gene expression [218]. With respect to HDACs, mice homozygous null for *Hdac5/9* have a high prevalence of embryonic lethality associated with a thinned myocardium and ventricular septal defects [83]. *Hdac4/7* double null embryos are also lethal, although the single nulls are viable [9]. Given the importance of both HATs and HDACs in regulating cardiac development and differentiated gene expression, it is not surprising that both also control cardiac hypertrophy in the adult heart. For example, transgenic mice with p300 overexpression develop cardiac hypertrophy, or show greater ventricular remodeling after injury [219,220]. In cultured cardiomyocytes, overexpression of p300/CBP by transfection promoted cellular growth while antisense or dominant negative p300/CBP attenuated agonist-induced growth [221]. Thus, p300/CBP activity are not only important for regulating differentiated gene expression in the heart, but they appear to function as necessary and sufficient regulators of hypertrophic growth itself, likely by facilitating the functional potency of key cardiac-expressed transcription factors.

Chromatin remodeling events mediated by class II HDACs are equally important in regulating cardiac hypertrophy, especially since many class II HDACs receive input from various signal transduction pathways through phosphorylation. For example, protein kinase D, PKC and CaMK have been identified as critical HDAC kinases that are activated by prohypertrophic signals, resulting in phosphorylation and subsequent nuclear export of class II HDACs [217]. Mechanistically, class II HDACs are recruited to critical genes that are involved in the regulation of muscle growth through physical interactions with transcription factors such as MEF2 [79–81]. *In vivo*, hypertrophy induced by activated calcineurin or pressure overload was associated with enhanced serine phosphorylation of HDAC5 and HDAC9 [84]. Moreover, expression of constitutively nuclear mutants of HDAC5 and HDAC9 inhibited agonist-induced hypertrophic growth in cultured neonatal cardiomyocytes [84]. *Hdac5* and *Hdac9* gene-deleted mice also showed spontaneous cardiac hypertrophy with age and enhanced hypertrophy in response to pathological stimuli [83,84].

Class I HDACs also appear to be critically important in regulating cardiac hypertrophy, although through a different mechanism compared with class II HDACs. For example, pharmacologic inhibition of class I HDACs significantly reduced cardiac hypertrophy after 2 weeks of pressure overload in the mouse [222]. Even the unselective HDAC inhibitors (inhibiting class I and II) trichostatin A and valproic acid reduced myocardial hypertrophy after angiotensin II or isoproterenol infusion, and in pressure overloaded mice and rats [222]. Although inhibition of class II HDACs should promote hypertrophy, the overall effect associated with global inhibition likely reflects the fact that class I HDACs predominate

compared with class II HDACs. Thus, both class I and II HDACs are critically tied to the cardiac hypertrophic response in the adult.

11. Conclusions and future directions

The adult cardiac hypertrophic growth program is a complex biologic process that involves the expression of many genes, a group of which represent genes with important developmental functions. Thus, there is a partial conservation in function whereby genes that promote embryonic and fetal heart growth are re-employed in the adult heart in response to disease stimuli. This paradigm is perhaps best characterized with respect to the numerous cardiac-expressed transcription factors that were discussed herein. Nearly all of the transcriptional regulators/modulators that were reviewed have dichotomous functions as both developmental control factors, as well as adaptive disease factors in the adult heart. In the future it will be important to use such knowledge as a means of adopting new therapeutic treatment strategies for adult heart disease, such as anti-hypertrophic agents directed at select cardiac transcription factors, or gene therapeutic strategies in which combinations of cardiac transcriptional regulators are used to regenerate areas of damaged human myocardium.

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Table 1

Summary of cardiac transcription factors as modulators of adult disease

Name	Binding Site	Disease functions in the heart	References
GATA4	5′-WGATAR-3′	• Overexpression induces cardiomyocyte hypertrophy *in vitro*	[22,23]
		• Transgenesis induces progressive cardiac hypertrophy *in vivo*	[22]
		• Conditional gene targeting reduces hypertrophic response *in vivo*	[16]
		• Increased cell death/apoptosis in gene-targeted heart *in vivo*	[16,24]
NFAT	5’-RGAAA-3’	• Constitutively nuclear NFATc4 mutant induces cardiac hypertrophy *in vivo*	[39]
		• Gene targeting of NFATc3, but not c4, reduces hypertrophic response *in vivo*	[41]
		• Overexression of dominant-negative mutant antagonizes hypertrophic response *in vitro*	[42]
NFκB	5′-GGGRNWTTCC-3′	• Cardiac inflammation (myocarditis) is blocked by overexpression of IκB *in vivo*	[52,53]
		• Inhibition with dominant negative mutant reduces cardiac hypertrophy *in vitro*	[56–59]
		• Gene targeting reduced hypertrophic growth induced by angiotensin II *in vivo*	[60]
		• Super-repressor mutant attenuated cardiac hypertrophy *in vivo*	[61,62]
MEF2	5′-CTAW$_4$TAG-3′	• Cardiac-specific overexpression of MEF2A or 2C induces dilated cardiomyopathy	[78]
		• Overexpression of MEF2A or 2C induces sarcomere degeneration *in vitro*	[78]
SRF	5′-CCW$_6$GG-3′	• Cardiac-specific overexpression induces hypertrophy with collagen deposition *in vivo*	[112]
		• SRF mutant causes postnatal chamber dilation with wall thinning *in vivo*	[113]
		• Conditional heart-specific deletion promotes progressive heart failure *in vivo*	[114]
		• Deletion in cardiomyocytes induces disorganization of contractile apparatus	[114,115]
		• Activity is inhibited in adult failing heart	[116,117]
Smads	5′-GYCTGTCT-3′	• Elevated after myocardial infarction and in response to cardiomyopathy *in vivo*	[141–146]
		• Association with cardiac fibrosis and collagen synthesis *in vivo*	[142,146,147]
		• Deletion of Smad4 induces basal cardiac hypertrophy and heart failure *in vivo*	[150]
		• Overexpression of Smad2 antagonizes cardiomyocyte hypertrophy *in vitro*	[151]
Nkx2.5	5′-TNAAGTG-3′	• Upregulated expression in response to hypertrophic stimulation	[168,169]
	5′-TTAATT-3′	• Overexpression (α-actin promoter) induces hypertrophic gene expression, but not cardiac hypertrophy	[170]
		• Dominant-negative mutant induces cardiac dysfunction and degeneration	[175]
		• Overexpression (α-MHC promoter) induces conduction abnormalities	[176]
Hand	5′-CANNTG-3′	• Downregulated expression of Hand1 in cardiomyopathic the human heart	[183]
		• Downregulation of Hand1/2 in PE-induced hypertrophy in the mouse	[184]
		• Upregulation of Hand2 by pressure-overload in the rat heart	[185]
Egr1	5′-TGCGGGGGCG-3′	• Gene targeting reduces cardiac hypertrophy induced by agonist stimulation *in vivo*	[192]
		• Nab1 (inhibitor of Egr1) transgenesis reduces pathologic cardiac hypertrophy *in vivo*	[193]
CREB	5′-TGANNTCA-3′	• Dominant-negative mutant induces dilated cardiomyopathy *in vivo*	[212]

N; any base, R; adenine or guanine, W; adenine or thymine, Y; cytosine or thymine.