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Current Perspective

Transcriptional Regulation of the Fetal Cardiac Gene Program

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Abstract. Reactivation of the fetal cardiac gene program in adults is a reliable marker of cardiac hypertrophy and heart failure. Normally, genes within this group are expressed in the fetal ventricles during development, but are silent after birth. However, their expression is re-induced in the ventricular myocardium in response to various cardiovascular diseases, and potentially plays an important role in the pathological process of cardiac remodeling. Thus, analysis of the molecular mechanisms that govern the expression of fetal cardiac genes could lead to the discovery of transcriptional regulators and signaling pathways involved in both cardiac differentiation and cardiac disease. In this review we will summarize what is currently known about the transcriptional regulation of the fetal cardiac gene program.

Keywords: transcription, cardiac remodeling, fetal cardiac gene, heart failure

1. Introduction

Hemodynamic overload induces a hypertrophic response in cardiac myocytes. The resultant cardiac hypertrophy is initially an adaptive response aimed at increasing cardiac output, but when the response is sustained it leads to cardiac decompensation and heart failure. Heart failure is a leading cause of morbidity and mortality around the world. This makes elucidation of the molecular mechanisms underlying the development of cardiac hypertrophy an important issue.

Cardiac hypertrophy is characterized by increases in cell size, protein synthesis, and sarcomeric assembly and alterations in gene expression, among which activation of the fetal gene program is one of the most consistent markers of cardiac hypertrophy (1, 2). Genes within this group include atrial and brain natriuretic peptide (ANP and BNP, respectively), fetal isoforms of contractile proteins (skeletal α-actin and β-myosin heavy chain), fetal type cardiac ion channels (hyperpolarization-activated cyclic nucleotide-gated channel and T-type Ca^{2+} channel) and some smooth muscle genes (smooth muscle α-actin and SM22α). All of these genes are abundantly expressed in fetal ventricles but are silent after birth (1, 3, 4). However, their expression is re-induced when the heart comes under pathological stress, and this expression is thought to play a key role in the molecular process underlying pathological cardiac remodeling (5). This suggests that the molecular pathways involved in the reactivation of fetal cardiac gene expression are closely linked to the adaptive/maladaptive molecular processes affecting cardiac muscle in response to pathological stress. Furthermore, clarification of the molecular mechanisms by which these fetal cardiac genes are regulated could lead to the identification of novel therapeutic targets for the treatment of heart failure. In this review, we provide a brief overview of what is currently known about the transcriptional regulation of the fetal cardiac gene program.

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Invited article

2. Transcriptional regulation of ANP and BNP gene expression

2.1. ANP

Studies using transgenic mice carrying a 500-bp or 2.4-kbp segment of the 5′ flanking region (5′-FR) of the human ANP gene, or a 638-bp or 3-kbp 5′-FR segment of the rat ANP gene, fused to a reporter gene have shown that these regions are sufficient to confer cardiac-restricted gene expression (6 – 8). Moreover, the ventricular activities of these 5′-FR segments are downregulated after birth, although the atrial activity remains high.

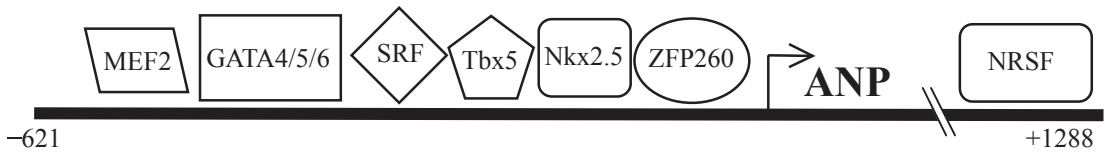

Fig. 1. Schematic representation of transcriptional factors that regulate ANP gene transcription.

These observations demonstrate that the proximal 5′-FR of the ANP gene is sufficient to recapitulate the spatial and temporal expression of the endogenous ANP gene and that this region contains sequences important for the regulation of ANP expression (9, 10).

The proximal 5′-FR of the ANP gene contains two CArG boxes, two NKEs, three TBEs, two GATA sites, an A/T-rich element, and a phenylephrine-responsive element (PERE), to which the transcription factors serum response factor (SRF), Nkx2.5, Tbx5, GATA4/6, myocyte enhancer factor (MEF)-2C, and zinc-finger protein (Zfp) 260 bind (Fig. 1) (11, 12). These elements contribute singly and/or cooperatively to the basal and inducible activation of ANP promoter activity in cardiac cells (13). That said, there are some differences in the expression pattern between the proximal 5′-FR of the ANP gene and the intact endogenous ANP gene, which suggests the presence of regulatory elements outside the proximal 5′-FR (11). For example, neuron-restrictive silencer element (NRSE), hypoxia-response element (HRE), and glucocorticoid responsive element (GRE), which are all located outside the proximal promoter, also reportedly mediate inducible ANP gene transcription (13 – 15). It should be noted that the ANP genes in humans and mice are, respectively, located 8 and 12 kbp downstream of the BNP gene on the same chromosome (human, chromosome 1; mouse, chromosome 4) (16, 17).

2.2. BNP

The 5′-FR of the BNP gene has also been well studied in order to understand the regulatory mechanisms governing the gene's cardiac-specific and inducible expression. A study using transgenic mice carrying a 1.8-kbp or 400-bp segment of the 5′-FR of the human BNP gene coupled to a luciferase gene (−1818hBNPluc and −400hBNPluc, respectively) showed that the proximal region of the human BNP promoter is sufficient to mediate ventricle-specific expression (18). In addition, BNP mRNA has an AT-rich region in its 3'-untranslated region (UTR), which makes the transcript unstable, implying post-transcriptional control of BNP expression (19, 20). Consistent with that idea, BNP mRNA has a shorter half-life than ANP mRNA.

Deletion analysis showed that the region extending from −127 to −40 in the human BNP 5′-FR confers cardiac-specific expression (21). This proximal region of the human BNP promoter contains potential GATA, M-CAT, and AP-1/CRE-like binding elements, which are conserved among humans, rats, and mice (Fig. 2) (22). All of these elements are known to regulate cardiac-specific gene expression and have been shown to mediate inducible BNP gene expression (13, 23). It was also recently shown that a short distance upstream (−193 to −184 in human BNP gene) of this region are CArG-like sequences, which are conserved among different species and mediate hypertrophic stimulus-inducible BNP gene transcription in a SRF-dependent manner (24). Other sites located in more distal regions of the human BNP 5′-FR contain NRSE (−552), shear stress responsive elements (SSREs) (−652, −641, and 161), thyroid hormone responsive element (TRE) (−1000), and nuclear factor of activated T-cells (NF-AT) binding site (−927), which also participate in the inducible activation of the human BNP promoter (Fig. 2) (13).

3. Transcriptional regulation of fetal contractile gene expression

3.1. *β*-Myosin heavy chain

The expression of sarcomeric proteins in the fetal heart undergoes major isoform switches at birth. In mouse ventricle, *β*-myosin heavy chain (MHC) is the predominant isoform in the developing heart, but it is replaced by *α*-MHC after birth. The change in the MHC isoform appears to be an important process via which the heart adapts its mechanical performance and efficiency to the postnatal circulation. During cardiac hypertrophy and heart failure, the expression of *β*-MHC gene is induced together with several other fetal cardiac genes. In humans, whose heart rates are slower than in mouse or rat, *β*-MHC is the predominant isoform in the ventricle from the fetus to the adult, but the ratio of the *α*- to *β*-MHC isoforms is reduced in failing ventricles, as is observed in the mouse heart. The *α*- and *β*-MHC genes are located in tandem on the same chromosome (human, chromosome 14; mouse, chromosome 11), although they are separated by about 4.5 kbp of intergenic sequence. Transcription of each gene is independently controlled but

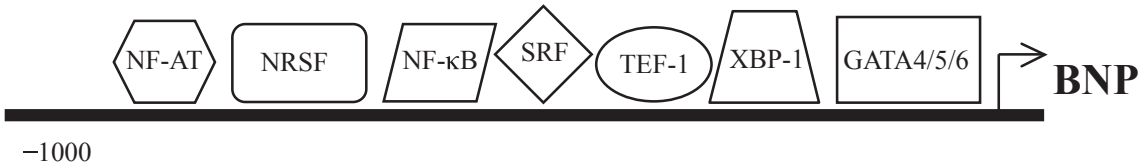

Fig. 2. Schematic representation of transcriptional factors that regulate BNP gene transcription.

coordinately regulated. In fetal ventricles, β-MHC gene is expressed as a part of the myogenic gene program, which is under the control of Nkx2.5, MEF-2C, and GATA4/5/6. After birth, the expression of β-MHC declines, while expression of α-MHC increases. Thyroid hormone is importantly involved in this isoform switch. The TRE located in the proximal promoter of α-MHC positively regulates the gene's expression after birth. By contrast, the TRE of β-MHC is a binding half-site located adjacent to a TATA box and negatively regulates that gene's expression. Under pathological conditions in the heart, activation of TEF-1-mediated transcription through multiple M-CAT elements located in the proximal 5′-FR of the β-MHC gene is induced by α_1-adrenergic stimulation. Ca^{2+}-mediated activation of calcineurin also appears to play an important role in the pathological induction of β-MHC gene expression by facilitating the translocation of NF-ATs to the nucleus, where they interact with GATA-4 and coordinately stimulate β-MHC gene transcription via GATA- and NF-AT-binding sites located in the proximal 5′-FR (25, 26). Recently a family of microRNAs (miRs) encoded by MHC genes was identified and are often referred to as MyomiRs. Three members of this family, miR-208a, miR-208b, and miR-499, are encoded by introns in the α-MHC (Myh6), β-MHC (Myh7), and Myh7b genes, respectively (27, 28). These miRs regulate a set of transcription factors and signaling molecules that govern MHC gene expression and modulate thyroid hormone signaling. Genetic deletion of miR-208a in mice blocks the reactivation of the β-MHC gene in response to pathological stress and restrains pathological remodeling (28). Thus the members of the MyomiR family appear to be components in an intricate regulatory loop affecting both MHC gene expression and cardiac remodeling.

3.2. Skeletal α-actin

Skeletal α-actin (SkA), which is a principal component of adult skeletal muscle thin filaments, is also a prominent actin isoform in the fetal heart. After birth, ventricular expression of SkA declines, and the gene is silent in the normal adult ventricular myocardium. In hypertrophied and failing hearts, however, SkA expression is reinduced. The proximal 5′-FR of SkA is sufficient to recapitulate its cardiac expression and inducible transcription (29). The TEF family proteins, SRF and Sp1 are required for hypertrophic stimulus-inducible expression of SkA and its re-induction in cardiac myocytes (30, 31), whereas YY-1 and NSRF negatively regulate SkA expression via binding sites, respectively, located in the 5′-FR and 3′-UTR (15, 30).

4. Transcriptional regulation of fetal ion channel gene expression

4.1. Hyperpolarization-activated cyclic nucleotide-gated channel 4

Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels 1 – 4 comprise an ion channel family that generates a current termed I_f or I_h (32, 33). In the adult heart, HCN channels are predominantly expressed in the conduction system, especially in the sinoatrial node, where HCN4 is the major isoform and controls cardiac rhythmicity (33). HCN channels are also expressed in ventricular myocytes, where HCN2 is the dominant isoform, but the levels of HCN channel expression in the adult ventricular myocardium are normally much lower than in the conduction system. Indeed, I_f is barely detectable in normal ventricular myocytes (33). During development, HCN channels are abundantly expressed in the fetal ventricular myocardium, but their ventricular expression progressively declines after birth, so that it is restricted to the conduction system in adult hearts (34). However, HCN channels, especially HCN2 and 4, are re-expressed in hypertrophied and failing ventricles in both rodents and humans (33, 35). Within the first intron of the HCN4 gene, there is a conserved binding site for NRSF, which may contribute to the repression of HCN4 expression in normal ventricular myocytes, as well as to the re-induction of HCN4 expression in response to pathological stimuli (15, 36). In addition, the HCN4 gene is positively regulated by AP-1 and MEF-2 proteins, whose binding sequences are both located within the gene's first intron (37).

4.2. T-type Ca^{2+} channel

During development, T-type Ca^{2+} channels are abundantly expressed in the embryonic ventricle, but their

expression is suppressed in the adult ventricle such that they are restricted to the conduction system (38, 39). However, T-type Ca^{2+} channels are re-expressed in hypertrophied and failing ventricles, and the resultant T-type Ca^{2+} currents ($I_{ca,T}$) are thought to be involved in pathological processes leading to systolic dysfunction and arrhythmogenesis (40). A transcriptional repressor, NSRF, negatively regulates CACNA1H, the gene encoding the cardiac T-type Ca^{2+} channel. The NSRF binding element, NRSE, is situated within its 2nd intron (14). Inhibition of NRSF-mediated repression may contribute to the increased cardiac expression of T-type Ca^{2+} channels under pathological conditions. In addition to the negative regulation by NRSF, CACNA1H gene expression is also positively regulated by Nkx2.5 (41).

5. Transcriptional regulation of smooth muscle gene expression

5.1. Smooth muscle α-actin

Smooth muscle α-actin (SMA) is the predominant actin isoform in the smooth muscle cells of the vascular and respiratory systems. SMA is also expressed in the fetal heart, but its expression declines during the final step in cardiac development and is completely absent from mature cardiac myocytes (42, 43). Ventricular SMA gene expression is re-induced in response to hypertrophic stimuli (3, 44), and the promoter-enhancer region extending from −2560 bp through the first intron (+2784 bp) of the SMA gene is sufficient to recapitulate the expression pattern of the endogenous SMA gene (45). This region contains three conserved CArG elements, a transforming growth factor β1 control element (TCE, a potential KLF family transcription factors-binding site), two E-boxes, and two MCAT elements (46). Among the transcription factors that can bind to these elements, SRF is known to play an important role in the pathological induction of SMA in cardiac myocytes (47).

5.2. SM22α

SM22α (also named transgelin1) is a member of the calponin family of proteins and is specifically expressed in mature smooth muscle cells. During embryogenesis, SM22α is transiently expressed in the cardiac and skeletal muscle lineages, before its expression is restricted to smooth muscle (4). The 445-bp SM22α promoter, which contains SRF-binding sequences (CArG), a SBE (a Smad-binding site), and a TCE (48, 49), is sufficient to direct the expression of a linked reporter gene in cardiac and skeletal muscle during development. In adult hearts, SM22α gene is re-expressed under certain pathological conditions in both mice and humans (24, 50). The precise transcriptional mechanisms mediating the re-expression of SM22α in cardiac myocytes in response to pathological stimuli remains unclear, although SRF may be involved, as with cardiac re-expression of SMA.

6. Conclusion

Reactivation of the fetal cardiac gene program is a reliable marker of cardiac hypertrophy and heart failure. Genes within this group are normally expressed in fetal ventricles during development, but are repressed after birth. However, their ventricular expression is re-induced when the myocardium is subjected to the stress of disease. Indeed, correspondence analysis between the gene expression profiles in the normal adult heart, failing heart, and fetal heart showed there to be a close relationship between the gene expression programs in fetal and failing human hearts (2). The transcriptional mechanisms that control each fetal cardiac gene have been studied, and a number of transcription factors have been found to participate in the regulation of fetal cardiac gene expression. In particular, SRF, GATA4/5/6, NF-ATs, TEF, MEF-2, and NRSF are commonly involved in the pathological induction of multiple fetal cardiac genes (13, 51). Reactivation of the fetal gene program would initially be an adaptive process to increase the contractility, excitability, and plasticity of cardiac myocytes in response to pathological stress, but when they are sustained, these genetic alterations contribute to the progression of maladaptive processes that ultimately lead to cardiac dysfunction. It is anticipated that further analysis of the molecular pathways modulating the aforementioned transcription factors and efforts to discover novel players involved in the expression of fetal cardiac genes will lead to the identification of potential new therapeutic targets for the treatment of heart failure.

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