A myocardin-adjacent lncRNA balances SRF-dependent gene transcription in the heart

Douglas M. Anderson,1,2,5 Kelly M. Anderson,1,2,5 Benjamin R. Nelson,2,5 John R. McAnally,2,5 Svetlana Bezprozvannaya,2,5 John M. Shelton,4 Rhonda Bassel-Duby,2,5 and Eric N. Olson2,3

1Department of Medicine, Cardiovascular Research Institute, University of Rochester Medical Center, Rochester, New York 14642, USA; 2Department of Molecular Biology, University of Texas Southwestern Medical Center, Dallas, Texas 75390, USA; 3Hamon Center for Regenerative Science and Medicine, University of Texas Southwestern Medical Center, Dallas, Texas 75390, USA; 4Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas 75390, USA

Myocardin, a potent coactivator of serum response factor (SRF), competes with ternary complex factor (TCF) proteins for SRF binding to balance opposing mitogenic and myogenic gene programs in cardiac and smooth muscle. Here we identify a cardiac lncRNA transcribed adjacent to myocardin, named CARDINAL, which antagonizes SRF-dependent mitogenic gene transcription in the heart. CARDINAL-deficient mice show ectopic TCF/SRF-dependent mitogenic gene expression and decreased cardiac contractility in response to age and ischemic stress. CARDINAL forms a nuclear complex with SRF and inhibits TCF-mediated transactivation of the promitogenic gene c-fos, suggesting CARDINAL functions as an RNA cofactor for SRF in the heart.

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Heart development and pathological remodeling are regulated by a network of transcription factors and noncoding RNAs that coordinate expression of genes involved in cardiomyocyte proliferation, differentiation, and contractility (Olson 2006; Miano 2010; Small and Olson 2011). SRF is a widely expressed transcription factor that binds the CArG-box DNA motif CC(A/T)6GG found in many muscle-specific and growth factor-inducible promoters (Shore and Sharrocks 1995; Miano 2010). In response to extracellular cues, SRF associates with diverse transcriptional coactivators to switch between opposing mitogenic and myogenic gene programs [Wang et al. 2004; Gualdrini et al. 2016]. Contractile and cytoskeletal genes are activated when SRF associates with the cardiac- and smooth muscle-specific coactivator myocardin [Myocd], or myocardin-related transcription factor-A [MRTF-A; MKL1] and myocardin-related transcription factor-B [MRTF-B; MKL2] in other tissues such as mammary myoepithelium and skeletal muscle [Wang et al. 2001, 2002a,b, 2003; Li et al. 2003; Wang and Olson 2004; Pipes et al. 2006]. Alternatively, the control of mitogen-activated cell signaling is dependent upon the association of SRF with members of the TCF family, including ELK-1, ELK-3, and ELK-4 [Shaw et al. 1989; Janknecht et al. 1993]. TCFs suppress myogenic gene expression by displacing Myocd/MRTFs from a common docking site on SRF; however, the mechanisms by which mitogenic genes are suppressed remain poorly understood. The coexpression of TCFs and Myocd/MRTFs in cardiomyocytes suggest that additional cofactors are required to counterbalance SRF-dependent gene programs in the heart.

Noncoding RNAs are an emerging class of transcriptional regulators of gene expression, many of which are expressed in tissue-specific patterns. Nucleotide polymorphisms in noncoding regions containing lncRNAs have long been associated with an increased risk for developing cardiovascular disease [Helgadottir et al. 2007; McPherson et al. 2007; Samani et al. 2007]. However, only recent in-depth functional studies have identified lncRNAs as important regulators of heart development [Grote et al. 2013; Klattenhoff et al. 2013; Anderson et al. 2016] and disease progression [Han et al. 2014; Wang et al. 2016]. LncRNAs play a variety of biological roles fundamental to regulating gene expression, including chromatin modification, protein synthesis, RNA processing, and gene silencing [Kaikkonen et al. 2011; Vance and Ponting 2014].

Given the vast number of noncoding RNAs that have been recently discovered in mammalian genomes, of which more than half are associated with chromatin [Werther and Ruthenburg 2015], lncRNAs represent an untapped reservoir of transcriptional cofactors for fine-tuning essential gene networks.

Here we characterize a cardiac lncRNA gene upstream of the Myocd locus that we named the myocardin-adjacent long noncoding RNA (CARDINAL). The CARDINAL promoter, conserved in both mouse and human genomes, is robustly activated by the cardiac transcription factors MEF2 and Myocd/MRTFs. Genetic disruption of CARDINAL in mice did not affect Myocd expression but resulted in ectopic expression of SRF-regulated mitogenic genes and decreased heart function with age and in response to ischemic stress. We show that CARDINAL localizes to chromatin in cardiomyocytes, forms a complex with SRF, and is sufficient to inhibit TCF-mediated transactivation of the SRF-target gene c-Fos. Furthermore, CARDINAL is significantly up-regulated with Myocd during heart failure in humans and mice, suggesting it plays a role in controlling the SRF-dependent cardiac gene networks required to maintain heart function and ventricular remodeling in response to injury or stress.

[Keywords: LINC00670, myocardin, SRF, long noncoding RNA; c-Fos, TCFs, ELK-1]

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Results and Discussion

Discovery of the cardiac lncRNA CARDINAL

In a bioinformatics screen for uncharacterized, cardiorestricted RNAs, we discovered a lncRNA transcribed upstream of myocardin in human [MYOCD] and mouse [Myocd] genomes [Fig. 1A]. We named this gene the myocardin–adjacent long noncoding RNA (CARDINAL). The human CARDINAL locus spans 87.4 kb and is comprised of four exons, terminating 28.8 kb upstream of the MYOCD transcriptional start site [Fig. 1A]. CARDINAL is transcribed in tandem with MYOCD on human chromosome 17 and is 2.8 kb [also named LINC00670].

In mice, two partially overlapping transcripts are annotated upstream of the Myocd locus on chromosome 11 [ENSMUST00000130362 and ENSMUST00000128453]. To determine the full-length CARDINAL sequence in mice, we performed rapid amplification of cDNA ends (RACE) using a primer specific to the ENSMUST0000128453 transcript. We found that the two annotated transcripts in mice are transcribed as a single ~3.0-kb RNA, encoded by six exons [Fig. 1A]. The full-length mouse CARDINAL locus spans 88.1 kb and terminates 7.6 kb upstream of the Myocd transcriptional start site [Fig. 1A]. The previously identified Myocd cardiac enhancer lies within the first intron of the mouse CARDINAL gene, ~31 kb upstream of the Myocd transcriptional start site [Fig. 1A; Creemers et al. 2006]. The genomic location of CARDINAL relative to Myocd was conserved in mice and humans, however, the exon organization was distinct, and only 57% nucleotide sequence homology was found between the mouse and human CARDINAL transcripts [Fig. 1A]. Promoter-specific H3K4Me3 histone modifications demarcate a single promoter site for CARDINAL in the developing and adult mouse heart [Supplemental Fig. S1A; Shen et al. 2012]. Northern blot analysis of multiple adult mouse tissues revealed a band corresponding to the predicted size of the full-length CARDINAL lncRNA in the heart [Supplemental Fig. S1B]. We detected no conserved protein-coding open reading frames within the CARDINAL transcript, and transcriptome-wide ribosome profiling and mass spectrometry on human heart tissues have not detected peptides originating from CARDINAL [van Heesch et al. 2019].

To compare the expression patterns of CARDINAL and Myocd, we performed in situ hybridization on mouse embryonic sections at embryonic day [E] 15.5. CARDINAL was detected exclusively in the heart, whereas Myocd was detected in the heart and the vascular and visceral smooth muscles of the dorsal aorta, lung, and intestines [Fig. 1B]. In adult mice, qRT-PCR detected robust CARDINAL expression in the atria and ventricles of the heart, and in the soleus, a slow-type skeletal muscle in which Myocd is absent [Fig. 1C]. In the developing heart, CARDINAL and Myocd were similarly enriched in cardiomyocytes and absent in cardiac fibroblasts [Supplemental Fig. S1C]. Among different immortalized mouse cell lines, CARDINAL was detected in mouse HL-1 cardiomyocytes [Supplemental Fig. S1D]. Subcellular fractionation of HL-1 cells showed enrichment of CARDINAL in the nuclear chromatin fraction, unlike two other RNAs, 18S and UpperHand (UPH), which were not associated with chromatin [Supplemental Fig. S1E]. Thus, CARDINAL is a chromatin-associated lncRNA that shares an overlapping but distinct expression profile with the neighboring transcription factor Myocd.

Figure 1. Discovery and expression of a myocardin–adjacent lncRNA (CARDINAL). [A] Diagram depicting the CARDINAL locus upstream of myocardin in mouse and human genomes. [CE] Myocardin cardiac enhancer. [B] Section in situ hybridization of mouse embryos at E15.5 using probes specific for CARDINAL and myocardin. Signal is pseudocolored red. [da] Diaphragm, [hrt] heart, [in] intestine, [lu] lung. Scale bars, 1 mm. [C] Quantitative real-time PCR analysis of CARDINAL and myocardin RNA expression across multiple adult mouse tissues. Values are expressed relative to liver.

Regulation of CARDINAL by MEF2 and Myocd/MRTFs

Previously, we reported that myocardin expression in heart and vascular smooth muscle is controlled by an upstream enhancer that requires binding of myocyte enhancer factor 2 [MEF2], a MADS-box transcription factor related to SRF [Creemers et al. 2006]. Myocardin is capable of activating its own enhancer, but unlike most other myocardin target genes, this activation occurs through Mef2, independent of SRF. Interestingly, we noted that the CARDINAL promoter contains two highly conserved A/T-rich sequences, located 155 and 205 nucleotides upstream of the CARDINAL transcription initiation site, that resemble MEF2 binding sites [Fig. 2A,B]. To determine whether MEF2 regulates CARDINAL, we generated a luciferase reporter using a 3.5-kb fragment of the CARDINAL promoter and first exon [3.5-kb CARDINAL-Luc]. The 3.5-kb CARDINAL-Luc reporter was highly responsive to MEF2, which trans-activated the reporter ~60-fold [Fig. 2C]. A 500-bp fragment of the CARDINAL promoter, retaining the two A/T-rich sequences, was
equally responsive to MEF2 [Fig. 2C]. Mutation of either MEF2 site in the 3.5-kb CARDINAL-Luc reporter reduced luciferase activity by about half, with mutation of both sites abolishing transactivation by MEF2 [Fig. 2C]. The 3.5-kb CARDINAL-Luc promoter was also robustly transactivated by the cardiac- and smooth muscle-specific isoforms of Myocd and the Myocd-related transcription factors MRTF-A and MASTR [Supplemental Fig. S2A]. These data suggest that CARDINAL is activated by pro-myoogenic cardiac transcription factor gene programs. To examine the regulation and expression of CARDINAL in vivo, we generated a transgenic reporter vector by fusing the 3.5-kb CARDINAL promoter sequence upstream of the β-galactosidase [LacZ] reporter gene (3.5-kb CARDINAL-LacZ). CARDINAL-LacZ transgenic reporter mice showed robust LacZ expression in the heart at embryonic, fetal, and adult time points [E8.5 to 2 wk] [Fig. 2D–F; Supplemental Fig. S2B–E]. In addition to the heart, LacZ staining was observed in the soleus but was absent from fast-type skeletal muscle, consistent with the expression of endogenous CARDINAL RNA [Fig. 2G]. LacZ staining was also detected in the developing mammary gland myoepithelium, a smooth muscle-like tissue whose development has been shown to be dependent upon MRTF-A expression [Supplemental Fig. S2F; Li et al. 2006]. Consistent with endogenous CARDINAL expression, LacZ staining was absent from the developing vascular and visceral smooth muscles, which abundantly express Myocd [Wang et al. 2001]. Simultaneous mutation of both MEF2 binding sites within the 3.5-kb CARDINAL-LacZ construct significantly attenuated LacZ expression in the heart, highlighting the importance of MEF2 as a requisite activator of the CARDINAL promoter in vivo [Supplemental Fig. S2G].

**Figure 2.** Regulation of CARDINAL by MEF2 in the heart. [A] Diagram showing conservation of the CARDINAL promoter and exon 1, with the two MEF2 binding sites [pink boxes]. [B] Sequence alignment of the two MEF2 sites in the CARDINAL promoter, highlighted in pink. [C] Luciferase reporter assay showing activation of CARDINAL promoter constructs by addition of MEF2 in transfected COS-7 cells. [Pink X] MEF2 site mutations. Data are represented as mean ± SEM. [D–G] β-Galactosidase staining of CARDINAL-LacZ transgenic reporter mice. [D] E10.5 embryos, [E] E15.5 fetus, and [F] and [G] adult heart, lung, [GPS] gastrocnemius-plantaris-soleus. [H] Heart, [lu] lung, [GPS] gastrocnemius-plantaris-soleus.

**Loss of CARDINAL results in ectopic SRF/TCF gene activation and decreased cardiac contractility in response to age and ischemic injury**

To characterize the function of CARDINAL in vivo, we inserted a Cre-ERT2 reporter followed by two polyadenylation cassettes into the first exon of the mouse CARDINAL locus. This strategy preserves enhancer or promoter sequences that may be required for CARDINAL or Myocd transcription, while prematurely terminating the CARDINAL RNA to generate a knockout (KO) allele [Fig. 3A]. The CARDINAL locus was modified using homologous recombination in murine embryonic stem cells. Blastocyst injection of targeted ES cells yielded chimeric founder mice, which were bred to C57BL/6 WT mice and genotyped using a PCR-based strategy [Supplemental Fig. S3A]. CARDINAL-Cre-ERT2 heterozygous mice, when crossed to a ROSA26-LacZ reporter line, showed tamoxifen-inducible LacZ expression in the heart, indicating the faithful expression of the modified locus [Supplemental Fig. 3B].

Homozygous CARDINAL mice showed no major morphological abnormalities or functional impairment through young adulthood [Fig. 3B,C]. However, echocardiography revealed a significant decline in left ventricular pumping efficiency in CARDINAL KO mice by 20 wk [Fig. 3C]. Quantitative PCR revealed the absence of CARDINAL in the heart and soleus of CARDINAL KO mice [Fig. 3D]. Surprisingly, the loss of CARDINAL and the termination of transcription through the CARDINAL locus had no significant impact on the expression of Myocd [Fig. 3E,F].

Chromatin-associated lncRNAs can function as regulators of gene transcription [Rinn and Chang 2012]; therefore, we profiled gene expression changes using RNA sequencing of the heart and soleus of CARDINAL KO and WT littermates at 8 wk of age. Consistent with our quantitative PCR data, CARDINAL was significantly down-regulated in both tissues, while the expression of Myocd was unchanged. Similarly regulated genes were found in the heart and soleus muscle of CARDINAL KO mice [Supplemental Fig. S3C,D; Supplemental Table S1]. The prototypical SRF-dependent immediate early [IE] genes c-Fos [Fos], Atf3, and Nr4a1 were significantly up-regulated in CARDINAL KO soleus and heart, with additional IE genes up-regulated within each tissue type [Supplemental Table S1]. The muscle-specific SRF targets, α-actin cytoskeletal genes Actc1 and Acta1 [Balza and Misra...
2006), were among the significantly down-regulated genes in both tissues (Supplemental Table S1). These findings reveal that SRF-dependent genes are altered in CARDINAL-KO tissues, independent of changes in myocardin expression.

In response to cardiac stress, Myocd and MRTF-A are up-regulated and required for hypertrophic growth and ventricular remodeling (Xing et al. 2006; Liao et al. 2011; Trembley et al. 2018). Similarly, CARDINAL was significantly up-regulated in mice and patients with heart failure following acute myocardial infarction (MI) (Supplemental Fig. S3E,F; Molina-Navarro et al. 2013). We subjected 8-wk-old CARDINAL KO and WT littermates to MI and measured cardiac function 1 d and 1 mo post-MI. In sham-operated mice, no differences in heart function or morphology were observed (Supplemental Fig. S3G). However, while cardiac function was similar between CARDINAL KO and WT mice prior to and 1 d after MI, CARDINAL KO mice had significantly reduced fractional shortening, increased scar formation, and increased LV internal diameter 1 mo post-MI compared with WT littermates (Fig. 3G,H, Supplemental Fig. S3H). These findings support a role for CARDINAL as an RNA cofactor that is required for normal heart function.

**CARDINAL interacts with SRF and regulates SRF-dependent gene transcription**

To test whether CARDINAL regulates SRF-dependent gene transcription, we measured the effect of CARDINAL on the expression of SRF/CArG-dependent promoters of the muscle-specific gene SM22 (TAGLN) and IE gene c-FOS in heterologous cell-based luciferase assays in COS-7 cells (Fig. 4A,B, Supplemental Fig S4A,B). Consistent with previous reports (Wang et al. 2004), robust activation of the SM22 promoter by Myocd was repressed by coexpression of ELK-1 (Fig. 4A). In contrast, ELK-1 activation of the c-FOS promoter was not inhibited by coexpression with CARDINAL in heterologous COS-7 cells. Consistent with previous reports (Wang et al. 2004), robust activation of the SM22 promoter by Myocd was repressed by coexpression of ELK-1 (Fig. 4A). In contrast, ELK-1 activation of the c-FOS promoter was not inhibited by coexpression with CARDINAL in heterologous COS-7 cells (Fig. 4A).
of Myocd, demonstrating the dominance of ELK1 on SRF-regulated promoters [Fig. 4B]. While CARDINAL did not alter Myocd or ELK1-mediated changes to the SM22 promoter activity, coexpression of CARDINAL was sufficient to repress ELK1-mediated activation of the c-FOS promoter [Fig. 4A,B]. These data demonstrate that unlike Myocd, CARDINAL can antagonize SRF/TCF-mediated gene expression.

To determine whether CARDINAL could mediate this repressive activity directly, we performed RNA immunoprecipitation (RIP) using FLAG-epitope tagged fusion proteins of SRF, Myocd, or ELK1 coexpressed with CARDINAL in COS-7 cells. CARDINAL formed a strong interaction with FLAG-SRF, weakly interacted with FLAG-ELK1, and did not interact with FLAG-Myocd [Fig. 4C]. SRF lacks a typical RNA binding domain; therefore, the interaction with CARDINAL may be through a multiprotein complex. SRF interacts with >70 cofactors, many of which associate with RNA [Castello et al. 2012]. As depicted in our model [Fig. 4D], we propose that CARDINAL promotes myogenic differentiation directed by Myocd and MRTFs in the heart by antagonizing TCF/SRF-mediated mitogenic gene transcription. Future studies on the biochemical nature of this interaction will shed light on the mechanistic role of CARDINAL as a novel RNA coregulator of cardiac gene transcription and contractility.

Materials and methods

Study approval

Animal work described was approved and conducted under the oversight of the University of Texas Southwesten Institutional Animal Care and Use Committee and by the University of Rochester Medical Center’s University Committee on Animal Resources.

Generation of CARDINAL KO mice

A targeting vector containing a CreERT2-2xP-A-Frt-Neo-Frt expression cassette was targeted to exon 1 of the CARDINAL locus in mice. The targeting vector was linearized and electroporated into 129SvEv-derived embryonic stem cells. One clone with a correctly targeted CARDINAL locus and first exon was expanded and injected into 3.5-d C57BL/6 blastocysts. Chimeric male mice were crossed to C57BL/6 females to achieve germline transmission of the targeted allele and genotyped using PCR. Genotyping primer sequences are in Supplemental Table S2.

Mouse model of myocardial infarction

C57BL/6 (WT) and CARDINAL KO mice at 10–12 wk of age underwent permanent ligation of the left anterior descending artery, as previously described [van Rooij et al. 2008]. Cardiac function and heart dimensions were evaluated by two-dimensional echocardiography on conscious mice using a VisualSonics Vevo 2100 system equipped with a 35-MHz transducer.

Generation of CARDINAL-LacZ transgenic mice

The 3.5-kb fragment of the upstream CARDINAL promoter and first exon (−3401 to +116) was cloned upstream of the β-galactosidase (LacZ) reporter gene in the vector BASIC-LacZ. Linearized LacZ reporter transgenes were injected into the pronuclei of fertilized oocytes using standard techniques.

Radiolabeled in situ hybridization

Radiosotopic in situ hybridization studies on sections were performed as previously described [Shelton et al. 2000]. Antisense RNA probe templates for CARDINAL or Myocd were generated using mouse heart cDNA and subcloned into pCRII TOPO (Life Technologies). Primer sequences are listed in Supplemental Table S2.

RNA immunoprecipitation

RNA-protein complexes from formaldehyde cross-linked HL-1 cell lysates were immunoprecipitated using anti-FLAG M2 conjugated agarose beads (Sigma Aldrich). RNA purification and expression analysis was performed as previously described [Anderson et al. 2016].

Cellular and subcellular fractionations

Neonatal cardiomyocytes were isolated from ∼50 postnatal day 1 (P3) C57BL/6 mice using the Neomix kit (Cellutron nc-6031) and fractionated as previously described [Anderson et al. 2016].

Northern blot analysis

Northern blots were performed using a commercially prepared adult mouse multissite RNA blot (Zyagen MN-MT-1) hybridized with a radiolabeled DNA probe specific to CARDINAL. Radiolabeled DNA probes for Northern and Southern blots were generated using a RadPrime kit (Life Technologies) [Supplemental Table S2].

Rapid amplification of cDNA ends (RACE)

The 5′ end of the mouse CARDINAL transcript in the heart was determined using Marathon RACE-ready adult mouse cDNA (Clontech). RACE-PCR was performed according to manufacturer’s recommended protocol, using primers specific to the 3′ CARDINAL fragment and the Marathon adapter primer 1 (AP1). The gene-specific primer used to amplify the 5′ sequence of CARDINAL is listed in Supplemental Table S2.

Statistical analysis

Results are expressed as mean ± SEM. Unpaired two-tailed Student t-test with Welch correction was performed to determine statistical significance. P-values of <0.05 were considered significant.

Competing interest statement

The authors declare no competing interests.

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References

Anderson KM, Anderson DM, McAnally JR, Shelton JM, Bassel-Duby R, Olson EN. 2016. Transcription of the non-coding RNA upperhand controls Hand2 expression and heart development. Nature 539: 433–436. doi:10.1038/nature20128

Balza RO Jr., Misra RP. 2006. Role of the serum response factor in regulating contractile apparatus gene expression and sarcomeric integrity in
cardiomyocytes. J Biol Chem 281: 6498–6510. doi:10.1074/jbc.M050487200
Castlelo A, Fischer B, Eichelbaum K, Horos R, Beckmann BM, Stein C, Davel NE, Humphreys DT, Preis T, Steinmetz LM, et al. 2012. Insights into RNA biology from an atlas of mammalian mRNA-binding proteins. Cell 159: 1393–1406. doi:10.1016/j.cell.2012.04.031
Cremers EE, Sutherland LB, McAnally J, Richardson JA, Olson EN. 2006. Myocardin is a direct transcriptional target of MEF2, Tead and Foxo proteins during cardiovascular development. Development 133: 4245–4256. doi:10.1242/dev.02610
Grote P, Wittler L, Hendrix D, Koch F, Währisch S, Beisaw A, Macura K, Blas G, Kellis M, Weber M, et al. 2013. The tissue-specific IncRNA Fendr is an essential regulator of heart and body wall development in the mouse. Dev Cell 24: 206–214. doi:10.1016/j.devcel.2012.12.012
Gualdimi F, Esaulti C, Horsswell S, Stawart A, Mathews N, Treisman R. 2016. SRF co-factors control the balance between cell proliferation and contractility. Mol Cell 64: 1048–1061. doi:10.1016/j.molcel.2016.10.016
Hans P, Li W, Lin CH, Yang J, Shang C, Nuenberg ST, Jin KK, Xu W, Lin CY, Lin CJ, et al. 2014. A long noncoding RNA protects the heart from pathological hypertrophy. Nature 514: 102–106. doi:10.1038/nature13596
Helgadottir A, Thorleifsson G, Manolescu A, Gretarsdottir S, Blondal T, Jonasdottir A, Jonasdottir A, Sigurdarsson S, Baker A, Palsson A, et al. 2007. A common variant on chromosome 9p21 affects the risk of myocardial infarction. Science 316: 1491–1493. doi:10.1126/science.1142842
Janknecht R, Ernst WH, Pindou V, Nordheim A. 1993. Activation of ternary complex factor Elk-1 by MAP kinases. EMBO J 12: 5097–5104. doi:10.1002/j.1460-2075.1993.tb06204.x
Kaikkonen MU, Lam MT, Glass CK. 2011. Non-coding RNAs as regulators of gene expression and epigenetics. Cardiogenes Res 90: 430–440. doi:10.1093/crv/cvrt097
Klattenhoff CA, Scheuermann JC, Surface LE, Bradley RK, Fields PA, Steinhausen ML, Ding H, Butty VL, Torrey L, Haas S, et al. 2013. Bravheart, a long noncoding RNA required for cardiovascular lineage commitment. Cell 152: 570–583. doi:10.1016/j.cell.2013.01.003
Li S, Wang DZ, Wang Z, Richardson JA, Olson EN. 2003. The serum response factor coactivator myocardin is required for vascular smooth muscle development. Proc Natl Acad Sci USA 100: 9366–9370. doi:10.1073/pnas.1233635100
Li S, Chang S, Qi X, Richardson JA, Olson EN. 2006. Requirement of a myocardin-related transcription factor for development of mammary myoepithelial cells. Mol Cell Biol 26: 5797–5808. doi:10.1128/MCB.00211-06
Liao XH, Wang N, Liu QX, Qin T, Cao B, Cao DS, Zhang TC. 2011. Myocardin-related transcription factor for development of mammary myoepithelial cells. Mol Cell Biol 26: 5797–5808. doi:10.1128/MCB.00211-06
Luo X, Wang N, Liu QX, Qin T, Cao B, Cao DS, Zhang TC. 2011. Myocardin-related transcription factor A induces cardiomyocyte hypertrophy. IUBMB Life 63: 54–61. doi:10.1002/iub.415
McPherson R, Pertsemlidis A, Kavaslar N, Stewart A, Roberts R, Cox DR, Proteas DA, Petesch LA, Tytluck KM, et al. 2016. Dysregulation of serum response factor co-factors control the balance between cell proliferation and contractility. Mol Cell 64: 1048–1061. doi:10.1016/j.molcel.2016.10.016
mRNA. Trends Genet 30: 348–355. doi:10.1016/j.tig.2014.06.001
van Hesch S, Witte F, Schneider-Luntz V, Schulz JF, Adami E, Faber AB, Kirchner M, Maatz H, Dahlut S, Sandmann CL, et al. 2019. The translational landscape of the human heart. Cell 178: 242–260.e19. doi:10.1016/j.cell.2019.05.010
van Rooij E, Sutherland LB, Thatcher JE, DiMaio JM, Naeseen RM, Marshall WS, Hill JA, Olson EN. 2008. Dysregulation of microRNAs after myocardial infarction reveals a role of miR-29 in cardiac fibrosis. Proc Natl Acad Sci USA 105: 13027–13032. doi:10.1073/pnas.0805088105
Wang DZ, Olson EN. 2004. Control of smooth muscle development by the myocardin family of transcriptional coactivators. Curr Opin Genet Dev 14: 558–566. doi:10.1016/j.gde.2004.08.003
Wang D, Chang PS, Wang Z, Sutherland L, Richardson JA, Small E, Krieg PA, Olson EN. 2001. Activation of cardiac gene expression by myocardin, a transcriptional cofactor for serum response factor. Cell 105: 851–862. doi:10.1016/S0092-8674(01)00404-4
Wang D, Passier R, Liu ZP, Shin CH, Wang Z, Li S, Sutherland LB, Small E, Krieg PA, Olson EN. 2002a. Regulation of cardiac growth and development by SRF and its cofactors. Cold Spring Har Symp Quant Biol 67: 97–106. doi:10.1126/sah.2002.67.97
Wang DZ, Li S, Hockemeyer D, Sutherland L, Wang Z, Schratt G, Richardson JA, Nordheim A, Olson EN. 2002b. Potentiation of serum response factor activity by a family of myocardin-related transcription factors. Proc Natl Acad Sci USA 99: 14655–14660. doi:10.1073/pnas.22561499
Wang Z, Wang DZ, Pipes GC, Olson EN. 2003. Myocardin is a master regulator of smooth muscle gene expression. Proc Natl Acad Sci USA 100: 7129–7134. doi:10.1073/pnas.123341100
Wang Z, Wang DZ, Hockemeyer D, McAnally J, Nordheim A, Olson EN. 2004. Myocardin and ternary complex factors compete for SRF to control smooth muscle gene expression. Nature 428: 185–189. doi:10.1038/nature02382
Wang Z, Zhang XJ, Ji YX, Zhang P, Deng KQ, Gong J, Ren S, Wang X, Chen I, Wang H, et al. 2016. The long noncoding RNA Chaer defines an epigenetic checkpoint in cardiac hypertrophy. Nat Med 22: 1131–1139. doi:10.1038/nm.4179
Werner MS, Ruttenburg AJ. 2015. Nuclear fractionation reveals thousands of chromatin-tethered noncoding RNAs adjacent to active genes. Cell Rep 12: 1089–1096. doi:10.1016/j.celrep.2015.07.033
Wong K, Zhang TC, Cao D, Wang Z, Antos CL, Li S, Wang Y, Olson EN, Wang DZ. 2006. Myocardin induces cardiomyocyte hypertrophy. Circ Res 98: 1089–1097. doi:10.1161/01.RES.0000218781.23144.3e