Title
A New Pathway for Sympathetic Cardioprotection in Heart Failure

Journal
Circulation Research, 117(7)

ISSN
0009-7330

Author
Simpson, Paul C

Publication Date
2015-09-11

DOI
10.1161/circresaha.115.307246

Peer reviewed

A New Pathway for Sympathetic Cardioprotection in Heart Failure

Paul C. Simpson

Sympathetic activation in heart failure (HF) is typically considered cardiotoxic. Indeed, class I recommended drugs in HF with reduced ejection fraction all inhibit direct or indirect effects of sympathetic activation. Contrary to this paradigm, Mayer et al[1] in this issue of *Circulation Research* provide evidence for a cardioprotective pathway mediated by activation of cardiac myocyte adrenergic receptors (ARs). This novel pathway involves β1- and α1-ARs, miR-212/132, and the epigenetic regulator, methyl CpG-binding protein 2 (MeCP2), the X-linked gene mutated in Rett Syndrome, a neurological disorder. The Figure outlines the model and the data from the article that support it.

Article, see p 622

Current Study

The initial focus of the study was mechanisms that facilitate reverse remodeling or cardiac recovery with unloading. Accordingly, the group used a clever approach of screening mRNAs that were differentially expressed between mouse transverse aortic constriction (TAC) and unloading by TAC reversal, ie, removing the constriction at a second surgery (rTAC). They identified MeCP2 as a gene that was repressed by TAC and normalized after TAC reversal. The same MeCP2 pattern was seen in humans with HF with reduced ejection fraction, where MeCP2 was repressed in failing hearts and normalized after unloading by left ventricular assist device. Among 30 genes with similar regulation in the human heart, MeCP2 was predominant in mouse myocytes versus nonmyocytes and was studied further. MeCP2 was also repressed in an α2-AR triple knockout, a mouse genetic model with high norepinephrine, implicating sympathetic activation in MeCP2 downregulation.

Expression studies focused on the linkage between norepinephrine elevation and MeCP2 repression identified the cluster miR-212/132, validated previously to target MeCP2, as having a pattern of regulation opposite to MeCP2. Thus, miR-212/132 were elevated in HF and were normalized by unloading and were predominant in myocytes versus nonmyocytes. The 2 miRs were upregulated by adrenergic activation, being induced by combined β1- and α1-AR stimulation with phenylephrine and isoproterenol in neonatal rat ventricular myocytes (NRVMs) in vitro and in the mouse heart in vivo, and in NRVMs by toxins that activate Gq and Gs. The same adrenergic stimuli that induced miR-212/132 concomitantly repressed MeCP2. MiR-132 repressed MeCP2 directly, in vitro and in vivo, by interacting with the MeCP2 3′untranslated region. Overall, the evidence was strong for a direct link between norepinephrine elevation, myocyte β1- and α1-AR stimulation, miR-212/132 induction, and MeCP2 repression.

To test the functional consequences of MeCP2 downregulation in HF, Mayer et al[1] used genetic gain and loss of function. The results were different from what might have been expected.

MeCP2 overexpression in a standard α-MyHC transgenic caused a severe cardiomyopathy with early mortality, so the team developed a cardiac inducible transgenic model (iTG), controlled by withdrawing doxycycline at weaning. This iTG model eliminated MeCP2 repression when TAC was done at the age of 8 to 12 weeks. Failure to repress MeCP2 with TAC was maladaptive. When compared with wild-type (WT) mice with TAC, failure to repress MeCP2 after TAC caused more hypertrophy, apoptosis, and fibrosis and worse cardiac function, with reductions in dp/dt and dobutamine response. Removal of the aortic constriction after 4 weeks in WT mice, in the rTAC model, caused a rapid reduction of hypertrophy and improvement in fractional shortening (FS), whereas in the MeCP2 iTG, reversal of hypertrophy and FS was delayed, indicating impaired reverse remodeling. An MeCP2 cardiac knockout (cKO) was established using MLC2a-Cre. MeCP2 cKO enhanced FS recovery in the rTAC model, without changing hypertrophy. Overall, the data suggested that failure to repress MeCP2 after TAC is maladaptive, and repression could be adaptive.

The team did extensive studies of gene expression and metabolism to investigate the molecular underpinnings of MeCP2 effects. Metabolic genes were downregulated in the MeCP2 iTG with TAC. Even in the absence of TAC, mitochondria in the MeCP2 iTG were abnormally located around the nucleus, rather than between myofibrils, and this abnormal location in the iTG was accompanied by reduced oxygen consumption and ATP synthesis in myocardial fibers and mitochondria in vitro. Peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α), a major mitochondrial regulator, was a direct target of MeCP2 in NRVMs, being downregulated by adenoviral MeCP2 expression and upregulated by MeCP2 knockdown; PGC1α was also downregulated by MeCP2 in the 2 transgenic models. Other genes of fatty acid metabolism had similar regulation. In short, MeCP2-mediated downregulation

From the VA Medical Center, San Francisco, CA; and University of California, Department of Medicine and CVRI, San Francisco.

Correspondence to Paul C. Simpson, MD, VA Medical Center (111-C-8), 4150 Clement St, San Francisco, CA 94121. E-mail paul.simpson@ucsf.edu

(*Circ Res*. 2015;117:592-595.
DOI: 10.1161/CIRCRESAHA.115.307246.)

***Circulation Research* is available at http://circres.ahajournals.org**
DOI: 10.1161/CIRCRESAHA.115.307246

of mitochondrial and metabolic genes could seemingly explain the maladaptive effects of failure to repress MeCP2 after TAC, at least in part.

Using an interesting new technique to isolate myocyte nuclei from cardiac tissue, involving an antibody to pericentriolar material 1 (PCM1), the team found that DNA methylation was not altered appreciably in WT mice with TAC, but that MeCP2 binding to methylated DNA was reduced, concomitant with the reduction in MeCP2 levels. Finally, immunoprecipitation in NRVMs suggested that MeCP2 interacted with HDAC1, a type I HDAC.

Overall, this prodigious study, reflecting the efforts of an impressive 29 coauthors, provided good evidence for a novel pathway of sympathetic cardioprotection in pressure-overload HF, as illustrated in the Figure.

MiR-212/132 and MeCP2: Background and Supporting Data

The new study focuses attention on 3 little-studied signaling molecules in cardiac biology, miR-212/132 and MeCP2. The Table provides background information.

Previous work on miR-212/132 and MeCP2 provides support for the model in the current study (Figure). Adrenergic agonists induce miR-212/132 in rat cardiac myocytes in vitro and in vivo.[2–4] The miRs can stimulate NRVM hypertrophy,[4,5] protect NRVMs from apoptosis by downregulating NCX,[6] reduce cardiac injury, and stimulate adaptive vasculogenesis.[7–10] Studies link reverse remodeling after MI to miR-132 induction and MeCP2 repression,[7] to an adaptive response in the bladder by miR-212/132 induction and MeCP2 repression,[11] and to liver fibrosis by miR 132 repression, MeCP2 induction, and peroxisome proliferator-activated receptor γ downregulation.[12] Downregulation of MeCP2 by siRNA reduces apoptosis after ischemia,[13] and MeCP2 overexpression in heart can be embryonic lethal,[14] in agreement with the current study.[1] Overall, past work suggests that miR-212/132 induction and MeCP2 repression might be a general adaptive mechanism in the heart and other organs.

Limitations of the Current Study

Despite the abundant data in the current study and support from previous work, certain limitations need to be considered. First, a previous study by one of the coauthors concludes that miR-212/132 are cardiotoxic, not cardioprotective.[4] Ucar et al[4] show that miR-212/132 repress Forkhead box O3 transcription factor (FoxO3) and are thereby sufficient and necessary for hypertrophy and reduce autophagy. MiR-212/132 overexpression causes HF, and systemic miR knockout or miR-132 antagomir protects from HF after TAC.[4] The current study does not address these contradictory findings about the effects of miR-212/132, other than to observe that isoproterenol/phenylephrine in vivo do not change FoxO3.[1] Speculatively, the discordance might be accounted for by cardioprotective effects of systemic miR antagomir or knockout via actions in immune or inflammatory cells,[15] whereas the current study is focused on miR-212/132 in myocytes only.

A second limitation is that most conclusions on the phenotypes caused by MeCP2 alterations are derived from overexpression, and it is not entirely clear how much MeCP2 protein is overexpressed. Furthermore, there are few data on the MeCP2 cKO. One is left to assume that the phenotype of the MeCP2 cKO is the converse of the iTG, and it would have been good to test this more completely.

Third, in this regard, the reduction in cardiac function with MeCP2 iTG and improvement with MeCP2 cKO are relatively subtle, and the proximate mechanisms are not clarified fully. For example, the current study finds an ≈10% area fibrosis in the MeCP2 iTG after TAC; this might not account for the 25% drop in FS with TAC; systolic function is preserved in the human heart with 10% area fibrosis.[16] The MeCP2 iTG after TAC increases apoptosis, but the fraction of TUNEL-positive cells is fairly small (0.04%) and increased only 2-fold from WT. Given the findings on metabolic genes and mitochondria, assays of myocardial high-energy phosphates in the iTG and cKO after TAC could have been informative. There are scant data of any kind in the cKO after TAC.

Overall, the last part of the model shown in the Figure needs to be taken as preliminary. Possibly miR-212/132 induction could be cardioprotective partly by repressing targets other than MeCP2 (Table).

Sympathetic Cardioprotection Pathways

The current study adds another pathway for sympathetic cardioprotection by cardiac myocyte AR activation. Notably, all of these are activation pathways, in contrast with the inhibition strategies that are the foundation of current class I HF drugs. Pathways from the β1-AR, which is thought to be

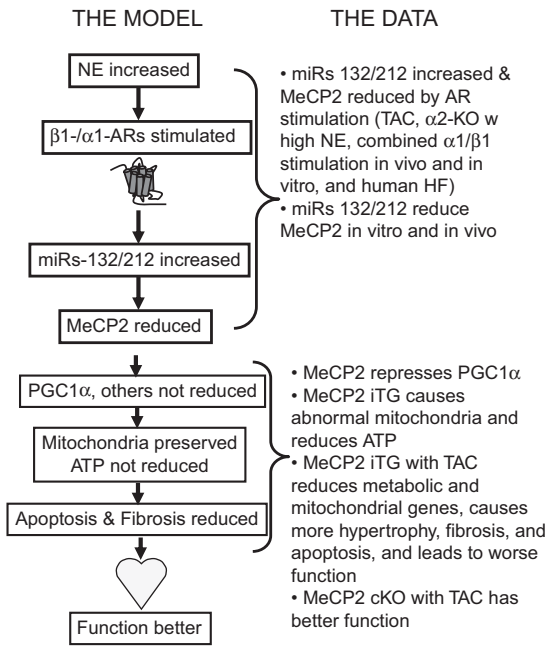

Figure. Left, The model suggested in the study by Mayer et al.[1] **Right**, The supporting data. Note that the beneficial effects of methyl CpG-binding protein 2 (MeCP2) repression are mostly deduced from the adverse effects seen with MeCP2 overexpression. AR indicates adrenergic receptor; cKO, cardiac knockout; HF, heart failure; iTG, inducible transgenic; KO, knockout; miR, microRNA; NE, norepinephrine; PGC1α, peroxisome proliferator-activated receptor γ coactivator 1α; and TAC, transverse aortic constriction.

Table. Background on MiR-212/132 and MeCP2

miR-132 and miR-212
Highly similar miRs with identical seed or targeting regions, transcribed from an intron of a noncoding gene on mouse chromosome 11[15]
Discovered and most abundant in brain, but expressed widely
Induced in cortical neurons by both ERK and cAMP pathways
Validated repression targets include MeCP2, HB-EGF (heparin binding epidermal growth factor-like growth factor), MMP9 (matrix metalloproteinase 9), Rb1 (retinoblastoma tumor suppressor), STAT4 (signal transducer and activator of transcription 4), the AT1R (angiotensin II type 1 receptor), Rem small GTPase and other GAPs (GTPase activating proteins), p300, SirT1 (sirtuin), the β2 subunit of the cardiac L-type calcium channel,[2] FoxO3 (Forkhead box O3 transcription factor),[4] and the inwardly rectifying potassium channel K(ir)2.1
Involved in many functions, especially neuronal development and activity, and also non-neuronal processes, including immunity and inflammation
MeCP2
Epigenetic regulator, defined by the NIH as regulating gene activity and expression independent of gene sequence; other epigenetic proteins are involved in lysine acetylation of histones by writers (HATs), erasers (HDACs), and readers (BETs, bromodomain and extraterminal proteins)
Discovered in 1992 as binding to methylated cytosines at CpG dinucleotides and can bind other sites as well[35]
Studied intensively as the causal mutation in Rett syndrome, an X-linked neuronal disorder affecting women primarily
At least 40 binding partners, acts primarily as a transcriptional repressor by recruiting corepressors such as HDACs, can also activate transcription, change alternate splicing, and alter miR processing
Very abundant and can alter phenotype by small changes in many genes

MeCP2 indicates methyl CpG-binding protein 2; miR, microRNA; and NIH, National Institutes of Health.

predominantly cardiotoxic with sustained activation,[17] are several. In addition to the current model (Figure), a pathway from the β1-AR and β-arrestin leads via GRK 5/6, Src, an MMP, HB-EGF, and the EGFR to ERK-mediated cardioprotection.[18] The same or a similar pathway activated by carvedilol at the β1-AR regulates processing of miRs,[19] some of which might be adaptive, eg, miR-150.[20] Another protective mechanism from the β1-AR revealed by PKA inhibition involves EPAC (exchange protein directly activated by cAMP), Rap1, Rac, and ERK activation.[21] However, there is a controversy whether EPAC is protective.[22] A body of evidence suggests cardioprotection by the β2-AR, possibly via a Gi, Gβγ, PI3K, Akt pathway[23] or alternately via a Gs mechanism.[24] However, some data argue against β2-mediated cardioprotection.[25] β3-AR activation can protect the heart from injury via NOS activation.[26] Finally, considerable data suggest that cardiac α1-AR activation, especially an α1A-ERK pathway,[27] is adaptive and protective in a variety of setting and species.[28]

Which of the above β1-, β2-, β3-, and α1-AR protective pathways are translatable to clinical use remains to be tested by time and reproduction among laboratories. Translation of the pathway outlined in the current study might be challenging because , as mentioned above, systemic miR-132 antagomir is protective. Furthermore, systemic reduction of MeCP2 activity can be cardiotoxic, with QT prolongation and ventricular tachycardia in the mouse MeCP2 knockout,[29] and subtle contraction abnormalities in patients with Rett syndrome.[30]

General Lessons From the Study

In addition to the novel pathway described, the study reminds of important principles in hypertrophy and HF. First, we often think that "bad" genes are upregulated in HF (eg, fetal genes) and "good" genes are downregulated (eg, α-MyHC or SERCA). Here, that was not the case; "good" genes were induced in HF (miR-212/132), and a "bad" gene was repressed (MeCP2). Second, FS improved with TAC removal in the MeCP2 cKO to a greater extent than in WT, despite the fact that overall hypertrophy did not change (HW/BW, myocyte CSA). This result suggests as in previous work that hypertrophy per se, ie, heart and myocyte size, is probably not the problem.[31–33] Rather, the problem is pathological signaling causing energy starvation, cell injury and death, fibrosis, and so on.

Third, it is sometimes thought that hypertrophy starts out as compensatory, and then becomes decompensated. The rTAC experiments show that most of the FS lost with TAC is recovered within 14 days of TAC reversal. This remarkable recovery suggests that compensatory signaling is not exhausted, even after 4 weeks TAC, a long time in a mouse, over 3 years in human equivalent time.[34] In other words, compensated and decompensated signaling seems to be going on in parallel. Decompensated "wins" in most cases, but compensatory signaling can be recruited by removing the injury (rTAC, left ventricular assist device), or perhaps by activating a protective pathway. That is one goal of medical therapy in HF.

Sources of Funding

This study was supported by the Department of Veterans Affairs and the National Institutes of Health. The Northern California Institute for Research and Education administers grants, and the Veterans Affairs Medical Center, San Francisco, California, provides resources.

Disclosures

Dr Simpson is involved in a company to study α1-adrenergic receptor agonism as therapy.

References

1. Mayer SC, Gilsbach R, Preissl S, et al. Adrenergic repression of the epigenetic reader MeCP2 facilitates cardiac adaptation in chronic heart failure. *Circ Res*. 2015;117:622–633. doi: 10.1161/CIRCRESAHA.115.306721.
2. Carrillo ED, Escobar Y, González G, Hernández A, Galindo JM, García MC, Sánchez JA. Posttranscriptional regulation of the β2-subunit of cardiac L-type Ca2+ channels by MicroRNAs during long-term exposure to isoproterenol in rats. *J Cardiovasc Pharmacol*. 2011;58:470–478. doi: 10.1097/FJC.0b013e31822a789b.
3. Hou Y, Sun Y, Shan H, Li X, Zhang M, Zhou X, Xing S, Sun H, Chu W, Qiao G, Lu Y. β-adrenoceptor regulates miRNA expression in rat heart. *Med Sci Monit*. 2012;18:BR309–BR314.

4. Ucar A, Gupta SK, Fiedler J, et al. The miRNA-212/132 family regulates both cardiac hypertrophy and cardiomyocyte autophagy. *Nat Commun*. 2012;3:1078. doi: 10.1038/ncomms2090.
5. Jentzsch C, Leierseder S, Loyer X, Flohrschütz I, Sassi Y, Hartmann D, Thum T, Laggerbauer B, Engelhardt S. A phenotypic screen to identify hypertrophy-modulating microRNAs in primary cardiomyocytes. *J Mol Cell Cardiol*. 2012;52:13–20. doi: 10.1016/j.yjmcc.2011.07.010.
6. Hong S, Lee J, Seo HH, Lee CY, Yoo KJ, Kim SM, Lee S, Hwang KC, Choi E. Na(+)-Ca(2+) exchanger targeting miR-132 prevents apoptosis of cardiomyocytes under hypoxic condition by suppressing Ca(2+) overload. *Biochem Biophys Res Commun*. 2015;460:931–937. doi: 10.1016/j.bbrc.2015.03.129.
7. Katare R, Riu F, Mitchell K, Gubernator M, Campagnolo P, Cui Y, Fortunato O, Avolio E, Cesselli D, Beltrami AP, Angelini G, Emanueli C, Madeddu P. Transplantation of human pericyte progenitor cells improves the repair of infarcted heart through activation of an angiogenic program involving micro-RNA-132. *Circ Res*. 2011;109:894–906. doi: 10.1161/CIRCRESAHA.111.251546.
8. Barile L, Lionetti V, Cervio E, Matteucci M, Gherghiceanu M, Popescu LM, Torre T, Siclari F, Moccetti T, Vassalli G. Extracellular vesicles from human cardiac progenitor cells inhibit cardiomyocyte apoptosis and improve cardiac function after myocardial infarction. *Cardiovasc Res*. 2014;103:530–541. doi: 10.1093/cvr/cvu167.
9. Lei Z, van Mil A, Brandt MM, Grundmann S, Hoefer I, Smits M, El Azzouzi H, Fukao T, Cheng C, Doevendans PA, Sluijter JP. MicroRNA-132/212 family enhances arteriogenesis after hindlimb ischaemia through modulation of the Ras-MAPK pathway. *J Cell Mol Med*. 2015;19:1994–2005. doi: 10.1111/jcmm.12586.
10. Zhao H, Wen G, Wen G, Huang Y, Yu X, Chen Q, Afzal TA, Luong le A, Zhu J, Shu Y, Zhang L, Xiao Q. MicroRNA-22 regulates smooth muscle cell differentiation from stem cells by targeting methyl CpG-binding protein 2. *Arterioscler Thromb Vasc Biol*. 2015;35:918–929. doi: 10.1161/ATVBAHA.114.305212.
11. Sadegh MK, Ekman M, Krawczyk K, Svensson D, Göransson O, Dahan D, Nilsson BO, Albinsson S, Uvelius B, Swärd K. Detrusor induction of miR-132/212 following bladder outlet obstruction: association with MeCP2 repression and cell viability. *PLoS One*. 2015;10:e0116784. doi: 10.1371/journal.pone.0116784.
12. Mann J, Chu DC, Maxwell A, Oakley F, Zhu NL, Tsukamoto H, Mann DA. MeCP2 controls an epigenetic pathway that promotes myofibroblast transdifferentiation and fibrosis. *Gastroenterology*. 2010;138:705–14, 714.e1. doi: 10.1053/j.gastro.2009.10.002.
13. Feng Y, Huang W, Wani M, Yu X, Ashraf M. Ischemic preconditioning potentiates the protective effect of stem cells through secretion of exosomes by targeting Mecp2 via miR-22. *PLoS One*. 2014;9:e88685. doi: 10.1371/journal.pone.0088685.
14. Alvarez-Saavedra M, Carrasco L, Sura-Trueba S, Demarchi Aiello V, Walz K, Neto JX, Young JI. Elevated expression of MeCP2 in cardiac and skeletal tissues is detrimental for normal development. *Hum Mol Genet*. 2010;19:2177–2190. doi: 10.1093/hmg/ddq096.
15. Wanet A, Tacheny A, Arnould T, Renard P. miR-212/132 expression and functions: within and beyond the neuronal compartment. *Nucleic Acids Res*. 2012;40:4742–4753. doi: 10.1093/nar/gks151.
16. Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Maleszewski JJ, Redfield MM. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. *Circulation*. 2015;131:550–559. doi: 10.1161/CIRCULATIONAHA.114.009625.
17. Whelan RS, Konstantinidis K, Xiao RP, Kitsis RN. Cardiomyocyte life-death decisions in response to chronic β-adrenergic signaling. *Circ Res*. 2013;112:408–410. doi: 10.1161/CIRCRESAHA.113.300805.
18. Noma T, Lemaire A, Naga Prasad SV, Barki-Harrington L, Tilley DG, Chen J, Le Corvoisier P, Violin JD, Wei H, Lefkowitz RJ, Rockman HA. Beta-arrestin-mediated beta1-adrenergic receptor transactivation of the EGFR confers cardioprotection. *J Clin Invest*. 2007;117:2445–2458. doi: 10.1172/JCI31901.
19. Kim IM, Wang Y, Park KM, Tang Y, Teoh JP, Vinson J, Traynham CJ, Pironti G, Mao L, Su H, Johnson JA, Koch WJ, Rockman HA. β-arrestin1-biased β1-adrenergic receptor signaling regulates microRNA processing. *Circ Res*. 2014;114:833–844. doi: 10.1161/CIRCRESAHA.114.302766.
20. Tang Y, Wang Y, Park KM, Hu Q, Teoh JP, Broskova Z, Ranganathan P, Jayakumar C, Li J, Su H, Tang Y, Ramesh G, Kim IM. MicroRNA-150 protects the mouse heart from ischaemic injury by regulating cell death. *Cardiovasc Res*. 2015;106:387–397. doi: 10.1093/cvr/cvv121.
21. Zhang X, Szeto C, Gao E, et al. Cardiotoxic and cardioprotective features of chronic β-adrenergic signaling. *Circ Res*. 2013;112:498–509. doi: 10.1161/CIRCRESAHA.112.273896.
22. Okumura S, Fujita T, Cai W, et al. Epac1-dependent phospholamban phosphorylation mediates the cardiac response to stresses. *J Clin Invest*. 2014;124:2785–2801. doi: 10.1172/JCI64784.
23. Talan MI, Ahmet I, Xiao RP, Lakatta EG. β_2 AR agonists in treatment of chronic heart failure: long path to translation. *J Mol Cell Cardiol*. 2011;51:529–533. doi: 10.1016/j.yjmcc.2010.09.019.
24. Woo AY, Song Y, Xiao R, Zhu W. Biased β_2-adrenoceptor signalling in heart failure: pathophysiology and drug discovery [published online ahead of print October 8, 2014]. *Br J Pharmacol*. doi: 10.1111/bph.12965.
25. Fajardo G, Zhao M, Urashima T, Farahani S, Hu DQ, Reddy S, Bernstein D. Deletion of the β2-adrenergic receptor prevents the development of cardiomyopathy in mice. *J Mol Cell Cardiol*. 2013;63:155–164. doi: 10.1016/j.yjmcc.2013.07.016.
26. Belge C, Hammond J, Dubois-Deruy E, et al. Enhanced expression of β3-adrenoceptors in cardiac myocytes attenuates neurohormone-induced hypertrophic remodeling through nitric oxide synthase. *Circulation*. 2014;129:451–462. doi: 10.1161/CIRCULATIONAHA.113.004940.
27. Huang Y, Wright CD, Merkwan CL, Baye NL, Liang Q, Simpson PC, O'Connell TD. An alpha1A-adrenergic-extracellular signal-regulated kinase survival signaling pathway in cardiac myocytes. *Circulation*. 2007;115:763–772. doi: 10.1161/CIRCULATIONAHA.106.664862.
28. Jensen BC, O'Connell TD, Simpson PC. Alpha-1-adrenergic receptors: targets for agonist drugs to treat heart failure. *J Mol Cell Cardiol*. 2011;51:518–528. doi: 10.1016/j.yjmcc.2010.11.014.
29. McCauley MD, Wang T, Mike E, Herrera J, Beavers DL, Huang TW, Ward CS, Skinner S, Percy AK, Glaze DG, Wehrens XH, Neul JL. Pathogenesis of lethal cardiac arrhythmias in Mecp2 mutant mice: implication for therapy in Rett syndrome. *Sci Transl Med*. 2011;3:113ra125. doi: 10.1126/scitranslmed.3002982.
30. De Felice C, Maffei S, Signorini C, Leoncini S, Lunghetti S, Valacchi G, D'Esposito M, Filosa S, Della Ragione F, Butera G, Favilli R, Ciccoli L, Hayek J. Subclinical myocardial dysfunction in Rett syndrome. *Eur Heart J Cardiovasc Imaging*. 2012;13:339–345. doi: 10.1093/ejechocard/jer256.
31. Perrino C, Naga Prasad SV, Mao L, Noma T, Yan Z, Kim HS, Smithies O, Rockman HA. Intermittent pressure overload triggers hypertrophy-independent cardiac dysfunction and vascular rarefaction. *J Clin Invest*. 2006;116:1547–1560. doi: 10.1172/JCI25397.
32. Crozatier B, Ventura-Clapier R. Inhibition of hypertrophy, per se, may not be a good therapeutic strategy in ventricular pressure overload: other approaches could be more beneficial. *Circulation*. 2015;131:1448–1457. doi: 10.1161/CIRCULATIONAHA.114.013895.
33. Schiattarella GG, Hill JA. Inhibition of hypertrophy is a good therapeutic strategy in ventricular pressure overload. *Circulation*. 2015;131:1435–1447. doi: 10.1161/CIRCULATIONAHA.115.013894.
34. Harrison DE. V. Life span as a biomarker. 2015: https://www.jax.org/research-and-faculty/research-labs/the-harrison-lab/gerontology/life-span-as-a-biomarker. Accessed August 28, 2015.
35. Lyst MJ, Bird A. Rett syndrome: a complex disorder with simple roots. *Nat Rev Genet*. 2015;16:261–275. doi: 10.1038/nrg3897.

KEY WORDS: Editorials ■ epigenenomics ■ heart failure ■ methyl-CpG-binding protein 2 ■ microRNAs ■ receptor, adrenergic

Circulation Research
JOURNAL OF THE AMERICAN HEART ASSOCIATION

A New Pathway for Sympathetic Cardioprotection in Heart Failure

Paul C. Simpson

Circ Res. 2015;117:592-595
doi: 10.1161/CIRCRESAHA.115.307246
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7330. Online ISSN: 1524-4571