Putting the Brakes on Cardiac Hypertrophy
Exploiting the NO–cGMP Counter-Regulatory System

George W. Booz

Abstract—We know a great deal about the receptors and signaling pathways in cardiomyocytes that contribute to hypertrophic growth. Although drugs that target them have proven effective in substantially reducing left ventricular hypertrophy and associated mortality, cardiovascular disease remains the leading cause of death in the West. Another approach may rest with exploiting naturally occurring regulators of maladaptive cardiac hypertrophy that have been identified in the past few years. These endogenous negative regulators can be grouped, for the most part, into those constitutively active but whose activity is decreased by hypertrophic stimulation, and those with little or no baseline activity that are activated by hypertrophic stimulation. Spanning both groups are 4 systems that converge on cyclic guanosine 3’, 5’-monophosphate (cGMP) generation, namely natriuretic peptides (ANP and BNP), kinins, nitric oxide (NO), and the angiotensin II type 2 receptor (AT2). Although holding promise as a means for restricting hypertrophy, each of these signaling molecules has certain limitations that need to be overcome. What follows is an overview of research over the past 2 years, much of it published in Hypertension, which has dealt with the antihypertrophic action of this particular group of endogenous signaling molecules. Understanding the function and regulation of the antihypertrophic NO–cGMP system offers the promise of novel therapeutic strategies for treating cardiac hypertrophy and heart failure. (Hypertension. 2005;45:341-346.)

Key Words: adrenergic antagonists • angiotensin II • kinins • natriuretic peptides • nitric oxide synthase • statins

V arious disease states that impose an additional workload on the heart, including hypertension and myocardial infarction, lead to left ventricular (LV) hypertrophy.1 The increase in LV mass is largely caused by increased size and protein content of cardiomyocytes and was once viewed as an adaptive response for maintaining cardiac output and tissue perfusion. After more than a decade of study, however, LV hypertrophy is recognized as a maladaptive response associated with untoward events, such as cardiomyocyte fetal gene re-expression, apoptosis, and interstitial fibrosis.1 Untreated, LV hypertrophy generally progresses to ventricular dilatation, systolic and diastolic contractile dysfunction, and heart failure. In fact, LV hypertrophy represents a well-established risk factor for cardiovascular mortality.2 Even the premise that cardiac hypertrophy is required to preserve heart function and normalize wall stress under conditions of pressure overload is challenged by recent studies.1,3,4

Drugs targeting receptors and signaling pathways that couple to cardiomyocyte hypertrophic growth are highly effective in reducing LV hypertrophy and associated mortality. Yet cardiovascular disease remains the leading cause of death in the West.5 Is there another strategy that could be used to control or reverse LV hypertrophy? An answer may rest with naturally occurring regulators of cardiac hypertrophy identified in the past few years, including those converging on cyclic guanosine 3’, 5’-monophosphate (cGMP) generation. Adopting the scheme of Hardt and Sadoshima,6 these endogenous negative regulators can be grouped into those constitutively active but whose activity is decreased by hypertrophic stimulation (kallikrein–kinin system and possibly endothelial nitric oxide synthase) and those with little or no baseline activity that are activated by hypertrophic stimulation (natriuretic peptides and AT2).

Cardiac cGMP and Nitric Oxide Formation
cGMP is generated in cardiomyocytes by soluble and particulate guanylyl cyclases. The catalytic activity of soluble guanylyl cyclases is increased by nitric oxide (NO) and, to a lesser degree, by carbon monoxide (CO).7,8 Although CO has also been shown to inhibit hypertrophy of cultured cardiomyocytes, cGMP is not involved.9 However, because NO and CO each potentially induces expression of both of the enzymes that produce them, a secondary involvement of cGMP in the actions of CO in vivo is possible.

NO is generated by nitric oxide synthase (NOS), all 3 isoforms of which are expressed in the heart.7 NOS1 and NOS3 are constitutively expressed and regulated by Ca2+, whereas NOS2 is not Ca2+-regulated and is induced in almost
any cell type with appropriate stimulation. Cardiomyocytes express all 3 isoforms, with spatial confinement helping to determine the function of Ca\(^{2+}\)-regulated isoforms.\(^{10}\) NOS3 localizes to caveolae, whereas NOS1 is present in the sarcoplasmic reticulum. Although NOS1 and NOS3 may have opposite effects on contractility, genetically engineered mice have linked both to an antihypertrophic response.\(^{10}\) NOS2 is expressed in the cytosol and, unlike the other isoforms, synthesizes large amounts of NO that are sustained. Chronic heart failure is associated with enhanced NOS2 myocardial expression; however, the contribution of NOS2 and sustained NO production to the development of heart failure is an area of intense debate.\(^{11}\) In any case, the multiple adverse effects of high NO levels produced by NOS2 overexpression in vivo appear to be attenuated by myoglobin, which effectively metabolizes NO.\(^{12,13}\) The observation that cardiac-specific NOS2 overexpression in myoglobin-deficient mice leads to cardiac hypertrophy, ventricular dilatation, and interstitial fibrosis indicates that the effect of NO on cardiomyocyte growth is dependent on spatial confinement and/or level of production.\(^{13}\)

**Atrial Natriuretic Peptide Signaling**

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) oppose the positive hemodynamic actions of the renin-angiotensin-aldosterone system by enhancing renal electrolyte and water excretion. Normally found in the heart in atrial myocytes, expression of these peptides (especially BNP) is upregulated in cardiac ventricles with pathological hypertrophy. Circulating levels of both ANP and BNP positively correlate with ventricular dysfunction, with plasma levels of BNP better reflecting the severity of heart failure.\(^{14}\) Both ANP and BNP also oppose the hypertrophic effect of angiotensin II (Ang II) and aldosterone on cardiomyocytes via the particulate guanylyl cyclase-A (GC-A) receptor and cGMP generation.\(^{15,16}\) In addition, mice with homozygous deletion of either the pro-ANP (\(Nppa^{−/−}\)) or GC-A genes exhibit cardiac hypertrophy under nonstress conditions and an exaggerated hypertrophic response with pressure overload.\(^{15}\) However, because germ-line GC-A or pro-ANP deletion is associated with a hypertensive phenotype, definitive evidence that ANP negatively affects cardiomyocyte growth in vivo was obtained only recently. Holtwick et al selectively inactivated the GC-A gene in cardiomyocytes.\(^{17}\) Despite arterial hypotension, these mice exhibited mild cardiac hypertrophy, characterized by enlargement of cardiomyocytes with no interstitial fibrosis, and an increased expression of several hypertrophy markers including ANP (which likely caused the hypotension). With pressure overload, cardiomyocyte-targeted GC-A hearts exhibited an enhanced hypertrophic response and marked impairment of cardiac function. The pro-ANP and GC-A knockout studies demonstrate that ANP negatively modulates cardiac growth under both physiological and pathophysiological conditions. As noted by Franco et al, however, humans are more likely to have partial rather than absolute ANP deficiency.\(^{18}\) They point out that an ANP gene polymorphism occurs with higher frequency in black salt-sensitive hypertensive subjects compared with normotensive or white hypertensive subjects. In addition, black salt-sensitive hypertensive subjects have blunted secretion of ANP in response to high salt intake. Therefore, Franco et al used ANP-heterozygous mice (\(Nppa^{+/−}\)) to assess the consequences of modest ANP reduction on cardiac function and remodeling after pressure overload. These mice had normal blood pressure and plasma ANP levels under nonstress conditions but plasma ANP levels that were intermediate between wild-type and ANP knockout mice with pressure overload. The finding that \(Nppa^{+/−}\) mice also showed greater pressure overload-induced cardiac hypertrophy and collagen deposition than wild-type mice, but less than knockout mice, implicates ANP as a natural antagonist of cardiac remodeling in response to pressure overload.

Signaling events responsible for the antihypertrophic actions of ANP/BNP on the heart have not been established but likely include cGMP-dependent protein kinases, cGMP-gated cation channels, and cGMP-regulated phosphodiesterases. Studies on cultured cardiomyocytes have shown that ANP opposes agonist-induced hypertrophy through cGMP formation and enhanced expression of MAPK phosphatase-1.\(^{19}\) In addition, activation of cGMP-dependent protein kinase type I (PKG I) by NO and cGMP was shown to inhibit the hypertrophic calcineurin–NFAT signaling pathway in cultured cardiomyocytes in part by inhibiting \(t\)-type Ca\(^{2+}\) channels.\(^{20}\) Intriguingly, long-acting dihydropyridine Ca\(^{2+}\) channel blockers were shown to inhibit cardiac hypertrophy induced by chronic NOS inhibition in the rat,\(^{21}\) although the involvement of \(t\)-type Ca\(^{2+}\) channels in cardiac hypertrophy is not established.

Wang et al identified several genes in the heart differentially regulated in \(Nppa^{−/−}\) and wild-type \(Nppa^{+/−}\) mice in response to pressure overload, including those encoding extracellular matrix proteins and extracellular matrix regulatory proteins.\(^{22}\) Their findings indicate that ANP also modulates cardiac remodeling by negatively regulating extracellular matrix deposition. In cultured cardiomyocytes, NO and cGMP also inhibit induction of calcineurin A subunit expression by a hypertrophic stimulus, which may be another means by which these agents inhibit calcineurin–NFAT pathway.\(^{23}\) Heinke et al recently examined hypertrophy-related genes regulated by NO in rat neonatal ventricular cardiomyocytes.\(^{24}\) In cells treated with endothelin-1, addition of the NO donor SNAP or NOS2 induction consistently downregulated the gene for muscle LIM protein (MLP) by both peroxynitrite formation and cGMP-dependent activation of PKG. MLP is a protein that helps to anchor sarcomeres to the sarcotendinous. Attenuation of MLP expression may explain in part the antihypertrophic actions of NO, because MLP overexpression induced some aspects of cardiomyocyte hypertrophy, whereas MLP downregulation suppressed hypertrophy.

Besides attenuating cardiac hypertrophy, both ANP and NO induce apoptosis of cardiomyocytes.\(^{25,26}\) The pro-apoptotic effect of ANP is observed at high concentrations and involves cGMP, whereas that of NO clearly involves, at a minimum, reaction with superoxide (\(O_2^−\)) to form peroxynitrite. How cGMP induces apoptosis is unclear and controversial. In a groundbreaking study, Wollert et al assessed the relative role of cGMP-dependent PKG I in the antihypertrophic and proapoptotic effects of NO on cardiomyocytes.\(^{27}\)
Using neonatal rat ventricular myocytes, these investigators showed that adenoviral gene delivery of PKG I enhanced the antihypertrophic effect of NO, without increasing susceptibility to apoptosis at higher concentrations of SNAP. Transgenic or knockout PKG I mice will have to be generated to show whether these findings are applicable to the adult heart exposed to pressure overload. If so, PKG I could represent a therapeutic target to selectively regulate cardiac hypertrophy.

The natriuretic peptides represent a compensatory mechanism of the body to reduce cardiac overload by reducing vascular resistance and effective blood volume. Because cardiac overload and hypertrophy are inexorably linked, upregulation of ANP and BNP can be viewed, as well as a negative feedback mechanism to limit cardiomyocyte growth at both the cellular and whole-body levels. Multiple lines of evidence indicate that ANP and BNP exert beneficial effects throughout the pathogenesis of heart failure. During the initial chronic phase, the peptides are responsible for maintaining sodium balance in the face of cardiac dysfunction and may ameliorate endothelial dysfunction by upregulating NOS3 and downregulating NOS2. In advanced congestive heart failure, which is characterized by sodium and water retention because of low cardiac output and reduced responsiveness of the kidneys to the natriuretic peptides, both animal and clinical studies have established that ANP and BNP continue to have beneficial effects.

**Kallikrein–Kinin System**

NO may arise from the actions of kinins on endothelial cells. Kinins, which are generated from enzymatic cleavage of kininogen by kallikreins, also inhibit cardiac hypertrophy. For example, B1-kinin receptor knockout mice exhibit progressive development of LV hypertrophy; conversely, rats overexpressing human tissue kallikrein have less cardiac hypertrophy and fibrosis than wild-type rats. In addition, the effectiveness of angiotensin-converting enzyme (ACE) inhibitors in attenuating cardiac hypertrophy in vivo has been attributed in part to increased kinin levels, because ACE is also a kinin-degrading enzyme.

Kinins exert most of their physiological effects through the B1 receptor, which activates NO/cGMP and prostacyclin/cAMP signaling pathways. Based on observations that the antihypertrophic effect of bradykinin on cultured cardiomyocytes is dependent on endothelium-derived NO and associated with increased cardiomyocyte cGMP, Rosenkranz et al investigated whether cGMP is essential for the antihypertrophic action of bradykinin. Using the isolated rat heart to better-approximate the situation in vivo, they compared the acute inhibitory effect of bradykinin on Ang II–induced hypertrophy with NO donor (sodium nitroprusside) and ACE inhibitor (ramiprilat). Bradykinin, which increased LV cGMP, prevented Ang II–induced increases in protein synthesis and ANP mRNA expression, as did sodium nitroprusside and ramiprilat. The antihypertrophic actions of both bradykinin and ramiprilat were attenuated by a guanylyl cyclase inhibitor. Moreover, a B2-kinin receptor antagonist prevented the antigrowth effect of ramiprilat. These results not only demonstrate that bradykinin has a direct inhibitory effect on Ang II–induced hypertrophy but also support the conclusion that the antihypertrophic actions of kinins and ACE inhibitors are mediated in part by an elevation of cardiomyocyte cGMP.

What is the impact of the kallikrein–kinin system on cardiac remodeling long-term? One such case would be after myocardial infarction (MI), when cardiac hypertrophy develops and progresses to congestive heart failure. To answer this, Agata et al injected rats via the tail vein 1 week after inducing MI with adenovirus harboring the human tissue kallikrein gene. They observed attenuated cardiac hypertrophy, fibrosis, and LV enlargement, and increased capillary density and enhanced endothelial function. Kallikrein expression also reduced myocardial caspase-3 activation and apoptosis while enhancing activity of Akt, a kinase linked to cell survival. The improvements in cardiac remodeling prevented the gradual decrease in cardiac output over the course of 6 weeks after MI and improved cardiac responses to dobutamine-induced stress. This study demonstrates that the kallikrein–kinin system can be recruited to prevent the progression to heart failure.

Gene polymorphisms that result in greater LV ACE activity or lower B2-kinin receptor expression are associated with exaggerated LV growth. Therefore, one would predict, that the role of kinins in the development of cardiac failure will be influenced by genetic background, as well as other factors such as age. In an intriguing study, Maestri et al compared the impact on the heart of B2-kinin receptor ablation in 2 strains of mice carrying either 1 (C57BL/6 mice) or 2 (129/J mice) renin genes. Increased renin expression in the latter is associated with higher basal blood pressure and increased sensitivity of pressure to salt and mineralocorticoids. B2-kinin receptor knockout in C57BL/6 mice resulted in age-dependent ventricular hypertrophy (cardiomyocyte enlargement and reparative fibrosis), as well as moderate impairment of systolic and diastolic performance. However, the severity of the alterations were less than seen in the 129/J strain, indicating that the kallikrein–kinin system interacts with various genetic determinants to impact on aging-related changes in cardiac structure and function. The involvement of NO/cGMP in the antihypertrophic actions of kinins in vivo will need to be established.

**Angiotensin II Type 2 Receptor**

Activation of the Ang II type 2 receptor (AT2) couples to NO/cGMP signaling in a number of contexts, either directly or indirectly through enhanced bradykinin formation or NOS3 expression. AT2 activation might be expected then to evoke an antihypertrophic effect on the heart, an outcome supported early on by studies on cultured cardiomyocytes. However, studies on AT2 knockout mice have yielded variable results, with one group actually reporting an obligatory role for AT2 in the development of pressure overload–induced hypertrophy. Therefore, the findings of a recent prospective study by AlFakhih et al are revealing. In patients with systemic hypertension, they observed an association between LV hypertrophy and a common intronic polymorphism of the AT2 gene, which results in less effective transcription. This finding is in keeping with the hypothesis that AT2 has antigrowth effects on the heart. Left unanswered, however, is
the cell type responsible and whether NO/cGMP signaling is involved.

Studies overexpressing AT2 specifically in cardiomyocytes have consistently failed to demonstrate an antihypertrophic effect of this receptor. In fact, ventricular myocyte–specific overexpression of AT2 leads to dilated cardiomyopathy and heart failure,41 likely because AT2 couples to additional signaling events besides NO/cGMP generation.37 Kurisu et al did not see any difference in the extent of cardiac hypertrophy induced by Ang II infusion in vivo between wild-type mice and transgenic mice with moderately increased cardiomyocyte AT2 level.38 However, transgenic mice did exhibit less perivascular fibrosis of the intramuscular coronary arteries. The attenuation of fibrosis was through a kinase/NO-dependent mechanism because it was eliminated by a bradykinin B2 receptor antagonist or NO synthase inhibitor. In addition, transgenic but not wild-type mice had markedly increased cardiac kininogenase activity after Ang II infusion.

Studies involving germ-line overexpression of AT2 are complicated by the importance of this receptor in cardiovascular development. To avoid this, Raizada et al used a lentiviral vector gene delivery system to increase AT2 in hearts of 5-day-old spontaneously hypertensive rats.42 This approach offers the advantage of high transduction efficiency and sustained gene expression. They found that AT2 transgene delivery prevented the increase in LV wall thickness of spontaneously hypertensive rats at 21 weeks after transduction, although blood pressure and cardiomyocyte AT1 expression did not differ between treated and control animals. The heart-to-body weight ratio was also decreased in treated spontaneously hypertensive rats compared with controls. These findings raise the possibility that this gene delivery approach could someday be exploited to treat different cardiac pathologies.

A role for AT2 in LV remodeling after MI seems more certain. MI studies performed with AT2–deficient mice have shown AT2 to have antihypertrophic effects43,44 or to contribute in part to the protection afforded by AT1 receptor blockers (ARBs).44 Xu et al found no differences in heart function or histology between AT2 knockout mice and wild-type littermates, or in progression of MI-induced cardiac dysfunction and remodeling.44 However, the beneficial effect of anARB, but not an ACE inhibitor, on cardiac function and remodeling after MI was attenuated in AT2 knockout mice. These data suggest that AT2 does not impact on cardiac function and morphology during development of heart failure after MI, but does make a contribution to the therapeutic effect of ARBs on MI–associated cardiac remodeling because of increased availability of Ang II.

Oishi et al also induced MI in AT2 knockout mice by ligating the left anterior descending artery; however, their study demonstrated a more active role for AT2 in cardiac remodeling after MI.45 Their results indicate that AT2 reduces early mortality rate after MI by protecting against early development of LV dilation. Rates of ventricular arrhythmia and cardiac rupture were similar between AT2 knockout and wild-type mice after MI, as were infarct size and blood pressure. However, on day 14 after MI, the mortality rate for knockout mice was higher than for wild-type mice. Knockout mice exhibited significantly greater LV/body weight ratios, as well as LV end-diastolic and end-systolic dimensions. Because myocyte cross-sectional areas were similar in the 2 strains after MI, the authors concluded that the greater LV dimensions and weight in AT2 knockout mice resulted from increased myocyte length and/or interstitial weight.

Xu et al44 and Oishi et al45 did not investigate whether the antihypertrophic action of AT2 after MI was mediated through NO/cGMP generation. Based on the observation that AT2 induces NOS3 expression in cultured cardiomyocytes through a calcineurin–dependent pathway, Brede et al investigated whether AT2–dependent NOS3 regulation affects cardiac remodeling in vivo after experimental myocardial injury.36 They used a cryoinfarction model to avoid variability in initial insult often seen with coronary artery ligation. Postinfarction remodeling was followed up for 4 weeks. AT2 knockout mice exhibited a greater increase in the heart weight-to-body weight ratio and the heart weight-to-tibia length ratio than control mice after the cryoprocedure. Cardiomyocytes of knockout mice had a greater increase in cross-sectional area than those of wild-type mice. Cardiac expression of NOS3 was significantly lower in AT2 knockout mice, as were cardiac cGMP levels. Moreover, in isolated cardiomyocytes, the antihypertrophic effect of AT2 was blocked by inhibiting NO production. This study demonstrates that AT2 has an antihypertrophic effect in cardiac remodeling after myocardial infarction through enhanced expression of NOS3. The study provides an explanation for the findings of others that the cardiac protective and antihypertrophic effects of an ACE inhibitor and ARB after MI are substantially diminished in NOS3 knockout mice compared with wild-type mice.45

As with the ANP and BNP, AT2 is reported to be upregulated with LV hypertrophy and heart failure.37 However, unlike the natriuretic peptides, evidence indicates that AT2 is not a simple negative feedback mechanism that can be easily exploited to reduce cardiomyocyte growth. Whereas short-term activation of AT2 may have beneficial effects in reducing cardiac hypertrophy, the study of Yan et al indicates that sustained AT2 expression (at least in ventricular myocytes) promotes development of dilated cardiomyopathy and heart failure.41

**Celioprol and Statins**

The clinically demonstrated ability of β-blockers to attenuate cardiac hypertrophy may be attributable in part to NO production. At a suppressor dose, the selective β1-blocker, celioprol, was shown to increase expression of cardiac NOS3 mRNA and protein in DOCA-salt rats, as well as to induce phosphorylation of a site that increases its activity.46 A follow-up study implicated augmented NO signaling in the ability of celioprol to inhibit pressure overload–induced cardiac hypertrophy and heart failure.47 Besides affecting NOS3 levels and activity, celioprol downregulated protein inhibitor of NOS (PIN).

The cholesterol-lowering drugs known as statins have been shown to reduce superoxide production by decreasing NAD(P)H oxidase expression and activity.48 Superoxide formation has been linked to cardiac remodeling, and statins have proven effective in preventing cardiac hypertrophy and
fibrosis resulting from pressure overload and MI. Superoxide formation has also been implicated in cardiac dysfunction and damage resulting from ischemia, sepsis, and cytokines, in part by combining with NO to form the powerful oxidant peroxynitrite. Speculatively, nitration of protein tyrosine residues by peroxynitrite might contribute to cardiac dysfunction by compromising protein structure and function. Recently, Nadruz et al examined the time course of nitrotyrosine production during development of pressure overload–induced cardiac hypertrophy and found the largest increases in myocardial nitrotyrosine correlated with the rapid phase of myocardial growth. Simvastatin attenuated cardiac hypertrophy, and this was accompanied by reduction in protein nitration and expression of NAD(P)H oxidase subunits. However, increased NAD(P)H oxidase expression and the amount of nitrated tyrosine were sustained up to 15 days, whereas increased expression of NOS isoforms was largely restricted to the early rapid phase of myocardial growth (3 to 7 days). Thus, enhanced superoxide, not NO, formation may be largely responsible for persistent protein nitration and, possibly, cardiac dysfunction.

Unresolved Issues and Perspectives
Although the NO–cGMP axis has been shown to attenuate cardiac hypertrophy, full therapeutic exploitation of this system faces at least 2 challenges, the first being concomitant untoward events. For NO, these would include reaction with superoxide, negative inotropic effects, and depressed mitochondrial respiration. NOS can also generate superoxide under certain conditions. Addressing these issues requires consideration of features of cardiac NOS such as isoform identity, spatial confinement, and substrate and cofactor availability. A better understanding of myocardial factors that protect against nitrosative stress is also needed. For natriuretic peptides, which are used in treating heart failure, receptor downregulation or uncoupling may limit their effectiveness in restricting cardiac hypertrophy.

The second challenge arises from the observation that although maladaptive signaling leading to LV hypertrophy may be inextricably linked to apoptosis and heart failure, survival pathways are likely to be activated as well. Thus, there is a need to parse the “good” from the “bad” signaling events occurring during maladaptive cardiac hypertrophy. For instance, although the calcineurin–nuclear factor of activated T-cells (NFAT) pathway is activated in pressure overload and overexpressing calcineurin results in cardiac hypertrophy that progresses to heart failure, calcineurin–NFAT has been linked to anti-apoptotic events. Thus, it is important to look at the effects of NO–cGMP-related signaling on all aspects of cardiac remodeling, including apoptosis, matrix deposition, gene expression, metabolism, and contractile function.

The second challenge raises the broader question of whether reversal of cardiac mass is beneficial in and of itself. Several studies have reported that increased cardiac mass is not necessary to maintain cardiac function in pressure overload, but in general this conclusion was reached after short-term observation. In addition, as noted by others, several genetic models have been generated that demonstrate marked “physiological” cardiac hypertrophy that is well-tolerated. Mass per se is undoubtedly too broad a target for therapeutic intervention in cardiac hypertrophy. After all, the pathogenesis of heart failure is complex, involving a host of events that include alterations in sarcomeric proteins, interstitial fibrosis, endothelial dysfunction, myocardial apoptosis, and abnormalities in cardiomyocyte cell–to-cell connection, excitation–contraction coupling, and mitochondrial morphology.

These unresolved issues highlight the need to move as far “downstream” as possible in developing therapeutic strategies based on exploiting any of the recently identified endogenous antihypertrophic systems, not just those involving NO–cGMP. In this regard, a recently identified growth-suppressing transcriptional pathway in cardiomyocytes holds promise as a therapeutic target. Whether this, or any as-yet-to-be identified, pathway is predominately an antimaladaptive hypertrophic pathway warrants investigation.

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References


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