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A friend within the heart: natriuretic peptide receptor signaling

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Commentary

Cardiovascular disease remains as the leading cause of death throughout the industrialized nations of the world. Central to this statistic is our current inability to effectively repair or otherwise reverse severe forms of cardiac dysfunction and pathologic remodeling that characterizes a failing heart. In response to hypertension, ischemic disease, valvular insufficiency, viral myocarditis, and genetic mutations in sacomeric proteins, the myocardium undergoes a hypertrophic growth phase as a compensatory measure aimed at maintaining cardiac output (1). However, longstanding cardiac hypertrophy often precipitates the development of more serious complications such as sudden death, fibrotic restrictive cardiomyopathy, dilated cardiomyopathy, and overt failure (2). Given the relatively poor clinical prognosis associated with end-stage heart failure, much investigation has focused on understanding the molecular underpinnings associated with the preceding hypertrophic remodeling stage. Indeed, a number of signaling networks have been identified that directly regulate the hypertrophic growth of cardiac myocytes (3). For example, neuroendocrine factors and/or intrinsic stretch-sensitive sensors, which signal through G protein–coupled receptors, receptor tyrosine kinases, or directly to second messengers, are thought to function as the initiating stimulus for the hypertrophic response (Figure 1). These upstream events promote signal transduction through a network of kinases and phosphatases thereby coordinating an increase in gene expression, total protein production and/or accumulation, and rRNA content, thus driving the hypertrophic growth of myocytes. However, as […]

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Cardiovascular disease remains as the leading cause of death throughout the industrialized nations of the world. Central to this statistic is our current inability to effectively repair or otherwise reverse severe forms of cardiac dysfunction and pathologic remodeling that characterizes a failing heart. In response to hypertension, ischemic disease, valvular insufficiency, viral myocarditis, and genetic mutations in sacomeric proteins, the myocardium undergoes a hypertrophic growth phase as a compensatory measure aimed at maintaining cardiac output (1). However, longstanding cardiac hypertrophy often precipitates the development of more serious complications such as sudden death, fibrotic restrictive cardiomyopathy, dilated cardiomyopathy, and overt failure (2). Given the relatively poor clinical prognosis associated with end-stage heart failure, much investigation has focused on understanding the molecular underpinnings associated with the preceding hypertrophic remodeling stage. Indeed, a number of signaling networks have been identified that directly regulate the hypertrophic growth of cardiac myocytes (3). For example, neuroendocrine factors and/or intrinsic stretch-sensitive sensors, which signal through G protein–coupled receptors, receptor tyrosine kinases, or directly to second messengers, are thought to function as the initiating stimulus for the hypertrophic response (Figure 1). These upstream events promote signal transduction through a network of kinases and phosphatases thereby coordinating an increase in gene expression, total protein production and/or accumulation, and rRNA content, thus driving the hypertrophic growth of myocytes. However, as is common to most biological response systems, a counter-regulatory network typically exists that buffers or antagonizes the forward cascade to permit selective reversal or graded responsiveness. Indeed, in this issue of the *JCI,* the article by Holtwick and colleagues provides definitive evidence for the existence of an antihypertrophic regulatory circuit within cardiac myocytes that functions to directly antagonize the hypertrophic growth response (4). This antihypertrophic regulatory circuit consists of the secreted atrial and B-type natriuretic peptides (ANP and BNP, respectively), and the ANP receptor guanylyl cyclase-A (GC-A).

Role of natriuretic peptide signaling in cardiovascular homeostasis

Three different natriuretic peptides have been characterized: ANP, BNP, and C-type natriuretic peptide (CNP), all of which function as secreted hormones involved in regulating blood pressure and blood volume through direct effects on the kidney and sys-

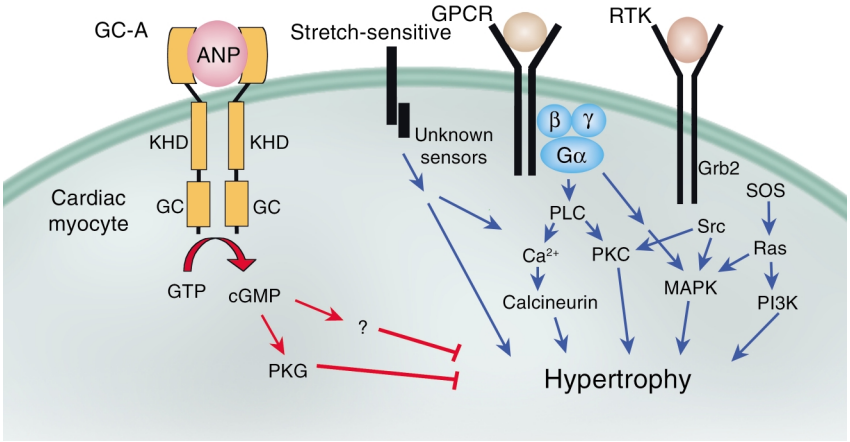

Figure 1
Cardiac myocytes have signaling pathways that agonize and antagonize hypertrophic growth. Neuroendocrine factors typically stimulate G protein–coupled receptors (GPCRs) and/or receptor tyrosine kinases (RTKs), which activate an array of intermediate signaling factors that ultimately drive the hypertrophic response. RTKs are typically coupled to adaptor and exchange factors such as Grb2 and SOS that induce Ras activation, or to Src kinase family members. GPCRs are typically coupled to G proteins that induce a number of signaling events such as phospholipase C (PLC) activation. Alternatively, cardiac myocytes may also directly respond to alterations in loading or stretching through internal sensors that link to prohypertrophic signal transduction cascades. In contrast, the action of ANP and BNP through the atrial natriuretic peptide receptor GC-A stimulates the production of cGMP and PKG, which function to antagonize hypertrophic growth within the cardiac myocyte itself. KHD, kinase-homology regulatory domain; GC, guanylyl cyclase catalytic domain.

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Nonstandard abbreviations used: atrial natriuretic peptide (ANP); B-type natriuretic peptide (BNP); guanylyl cyclase-A (GC-A); C-type natriuretic peptide (CNP); cGMP-dependent protein kinase (PKG).

temic vasculature (5–7). ANP and BNP are each produced within the heart and secreted in response to atrial stretching that typifies an increase in blood volume. The release of ANP and BNP from the heart has the most immediate biologic effect of increasing electrolyte and water excretion in the kidney by functionally antagonizing the "salt-sparing" role of the renin-angiotensin-aldosterone system, thus reducing blood volume and pressure (5–7). However, ANP and BNP also regulate the permeability of the systemic vasculature, cellular growth, cellular proliferation, and more recently, cardiac hypertrophy (5–7). These actions of ANP and BNP are primarily mediated by the GC-A receptor, although guanylyl cyclase-B, which primarily binds CNP, is thought to be involved in the central control of total body fluid homeostasis (5–7). GC-A is a type I transmembrane receptor that dimerizes and binds ANP and BNP through an extracellular ligand-binding domain (Figure 1). GC-A also contains an intracellular kinase-homology regulatory domain and a guanylyl cyclase catalytic domain (GC) (Figure 1). Ligand-induced GC-A activation generates cGMP inside the responding cell, which in turn activates signal transduction factors such as low and high affinity cGMP-dependent protein kinases (PKGs) (Figure 1).

ANP/BNP-GC-A signaling antagonizes cardiac hypertrophy

Within the past few years, the ANP/BNP-GC-A signaling circuit has been implicated as an intrinsic regulator of cardiac hypertrophy, potentially serving as the postulated counter-regulatory signaling circuit within the heart. The potential importance of this signaling system to cardiovascular homeostasis is underscored by the observation that hypertrophy and heart failure are almost always associated with increased ANP and BNP expression within the heart proper, as well as with increased circulating levels of these two peptides in the blood (5–7). Indeed, total levels of circulating ANP and BNP are strongly correlated with the degree of ventricular dysfunction and eventual mortality (8). To mechanistically assess the potential role of natriuretic peptide receptor signaling on cardiac myocyte biology, two separate groups generated transgenic mice overexpressing components of this signaling circuit. Klinger and colleagues generated mice expressing ANP under the control of the transthyretin promoter, while Kishimoto and colleagues generated transgenic mice expressing GC-A specifically within the heart, each of which showed significantly smaller hearts (9, 10). Conversely, reduction or elimination of *ANP/GC-A* signaling in rodents by gene targeting or due to genetic polymorphism was associated with significant cardiac hypertrophy at baseline (10–16). Moreover, treatment of isolated neonatal cardiomyocytes in culture with ANP reduced agonist-induced hypertrophy (17–19). Collectively, these results strongly implicate ANP/BNP-GC-A signaling as an antihypertrophic regulatory circuit in the heart. Events associated with GC-A signaling, such as increases in cGMP or activation of PKG, have also been associated with a reduction in cardiac myocyte hypertrophy (17, 20). In fact, inhibition of PKG I in cardiac myocytes enhanced agonist-induced hypertrophy while upregulation of PKG I signaling by adenoviral-mediated overexpression antagonized calcineurin-nuclear factor of activated T lymphocyte signaling, a known prohypertrophic regulatory pathway (20). Taken together, these results suggest that ANP/BNP-GC-A signaling antagonizes myocyte growth through a cGMP-PKG–dependent pathway.

GC-A antihypertrophic signaling is myocyte autonomous

While a reasonable data set has emerged suggesting an antihypertrophic role for ANP/BNP-GC-A signaling within the heart, a significant limitation has persisted. Each of the studies discussed above could also be partially explained by noncardiac effects that secondarily impact the hypertrophic response. For example, loss of *BNP* or *GC-A* in traditionally targeted mouse models promoted significant hypertension, which induced a secondary myocardial growth response due to increased afterload (11, 12, 14, 15, 21). However, the report by Holtwick and colleagues definitively lays this issue to rest (4). These authors generated a loxP-targeted *GC-A* allele in mice, which was subsequently deleted in a cardiac-specific manner using α-myosin heavy chain-Cre–expressing transgenic mice. This selective loss of the *GC-A* receptor in the heart invoked a hypertrophic growth response at baseline, demonstrating that GC-A signaling normally plays a homeostatic role in maintaining cardiac mass within a given range. Moreover, afterload-induced cardiac hypertrophy was significantly elevated over similarly treated wild-type controls, indicating that GC-A signaling normally limits the full extent of stimulated hypertrophic growth. Interestingly, cardiac-specific *GC-A*–deleted mice showed a secondary increase in circulating ANP levels that actually decreased blood pressure, which would normally reduce cardiac mass, although *GC-A* mice had increased mass and an exaggerated load-induced growth response. Taken together with past studies, this report by Holtwick and colleagues represents the final proof that ANP/BNP-GC-A signaling functions as a myocyte intrinsic counter-regulatory growth circuit in the heart (Figure 1).

The results discussed above support the potential clinical relevance of ANP and BNP therapeutics in humans with heart failure. Indeed, nesiritide, a recombinant form of human BNP has shown short-term hemodynamic and symptomatic improvements in patients with acute decompensated heart failure (22). Based on the conclusive results of Holtwick and colleagues (4) and the relatively safe profile already observed for nesiritide in clinical trials, it is reasonable to predict that natriuretic peptide–based therapies might also benefit earlier stages of heart failure or even preceding hypertrophic disease, provided an adequate delivery platform was devised. However, such approaches must be considered in the context of two important concerns. First, pathologic hypertrophy and heart failure are already associated with a significant upregulation in ANP and BNP expression within the heart, which increases with disease severity. Since many forms of pathologic hypertrophy and heart

failure are progressive, it suggests that this counter-regulatory mechanism within the heart is limited and ultimately fails to provide long-term protection. Secondly, we must consider whether or not it will ultimately be beneficial or detrimental to treat (i.e., prevent) cardiac hypertrophy in response to pathologic conditions such as hypertension or valvular disease. In other words, would cardiac decompensation simply occur sooner if one blocks the hypertrophic phase of the response?

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Double target for tumor mass destruction

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As the growth of most cancers is dependent on the growth of tumor blood vessels, inhibition of tumor angiogenesis may provide an efficient strategy to slow down or block tumor growth. The possibility of selectively targeting angiogenic vasculature in a tumor mass depends on molecular, cellular, and structural differences between the tumor vessels and their normal counterparts (Figure 1). Tumor cells, like normal cells, need to be located close to the blood vessels serving their metabolic demands to the extent that in solid tumors every endothelial cell in a tumor vessel is considered to support several concentric layers of tumor cells (1). A hypoxic tumor generates its own microcirculation mainly via the hypoxia-inducible factor (HIF) complex, which is activated by inhibition of its oxygen-dependent prolyl hydroxylation and proteasomal destruction (2). This leads to increased transcription of several hypoxia-induced genes. One such gene encodes VEGF, which activates endothelial cell (EC) responses during angiogenesis in coordination with, for example, matrix adhesion events. Studies of the signaling pathways of VEGF receptors, integrins, and cadherins have provided new antiangiogenic strategies for inhibition of tumor growth, and inhibition of VEGF-C and VEGF-D signals that stimulate lymphangiogenesis seems to inhibit lymphatic metastasis in mice (3). One of the most striking new developments in antiangiogenesis research concerns the inflammatory cells and pericytes (PCs) associated with the tumor vasculature. The new findings presented in this issue of the *JCI* by Bergers and collaborators suggest that the PCs of tumor blood vessels and their signaling mechanisms via the PDGFR-β are functionally important for the maintenance of tumor blood vessels (4). These findings add another constituent cell type of tumor stroma to the list of anticancer targets.

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Nonstandard abbreviations used: hypoxia-inducible factor (HIF); endothelial cell (EC); pericyte (PC).