Hypertrophy of the Heart
A New Therapeutic Target?

Norbert Frey, MD; Hugo A. Katus, MD; Eric N. Olson, PhD; Joseph A. Hill, MD, PhD

Abstract—Recent studies call into question the necessity of hypertrophic growth of the heart as a "compensatory" response to hemodynamic stress. These findings, coupled with recent progress in dissecting the molecular bases of hypertrophy, raise the prospect of suppressing hypertrophy without provoking circulatory insufficiency. In this article, we focus on signaling pathways that hold promise as potential targets for therapeutic intervention. We also summarize observations from animal models and clinical trials that suggest benefit from an antihypertrophic strategy. **(*Circulation*. 2004;109: 1580-1589.)**

Key Words: hypertrophy ■ heart failure ■ signal transduction

Cardiac hypertrophy is an adaptive response to pressure or volume stress, mutations of sarcomeric (or other) proteins, or loss of contractile mass from prior infarction. Hypertrophic growth accompanies many forms of heart disease, including ischemic disease, hypertension, heart failure, and valvular disease. In these types of cardiac pathology, pressure overload–induced concentric hypertrophy is believed to have a compensatory function by diminishing wall stress and oxygen consumption.[1–3] At the same time, ventricular hypertrophy is associated with significantly increased risk of heart failure and malignant arrhythmia.[4,5]

In the 1960s, Meerson and colleagues[6] divided hypertrophic transformation of the heart into 3 stages: (1) developing hypertrophy, in which load exceeds output, (2) compensatory hypertrophy, in which the workload/mass ratio is normalized and resting cardiac output is maintained, and (3) overt heart failure, with ventricular dilation and progressive declines in cardiac output despite continuous activation of the hypertrophic program. The late-phase "remodeling" process that leads to failure is associated with functional perturbations of cellular Ca^{2+} homeostasis[7] and ionic currents,[8,9] which contribute to an adverse prognosis by predisposing to ventricular dysfunction and malignant arrhythmia. Significant morphological changes include increased rates of apoptosis,[10] fibrosis, and chamber dilation. Even though the dichotomy between adaptive and maladaptive hypertrophy has been appreciated for more than a century,[11] mechanisms that determine how long-standing hypertrophy ultimately progresses to overt heart failure are poorly understood.

At the cellular level, cardiomyocyte hypertrophy is characterized by an increase in cell size, enhanced protein synthesis, and heightened organization of the sarcomere. Classically, 2 different hypertrophic phenotypes can be distinguished: (1) concentric hypertrophy due to pressure overload, which is characterized by parallel addition of sarcomeres and lateral growth of individual cardiomyocytes, and (2) eccentric hypertrophy due to volume overload or prior infarction, characterized by addition of sarcomeres in series and longitudinal cell growth.[12] At the molecular level, these changes in cellular phenotype are accompanied by reinduction of the so-called fetal gene program, because patterns of gene expression mimic those seen during embryonic development.

Hypertrophy that occurs as a consequence of pressure overload is termed "compensatory" on the premise that it facilitates ejection performance by normalizing systolic wall stress. Recent experimental results, however, call into question the necessity of normalization of wall stress that results from hypertrophic growth of the heart. These findings, largely from studies in genetically engineered mice, raise the prospect of modulating hypertrophic growth of the myocardium to afford clinical benefit without provoking hemodynamic compromise.

To accomplish this goal, it is essential to identify molecular events involved in the hypertrophic process, a topic reviewed recently,[13,14] and to identify commonalities and differences in the signaling systems that promote pathological hypertrophy versus physiological hypertrophy.[15] Especially critical is elucidation of mechanisms underlying the maladaptive features of hypertrophy, such as arrhythmogenicity and transformation to heart failure. Here, we summarize recent observations from animal models and clinical trials that identify signaling cascades that hold promise as potential targets for therapeutic intervention. We focus on pathways that have

From the Department of Cardiology (Innere Medizin III), University of Heidelberg (N.F., H.A.K.), Heidelberg, Germany, and Departments of Molecular Biology (E.N.O., J.A.H.) and Internal Medicine (J.A.H.) and the Donald W. Reynolds Cardiovascular Clinical Research Center (E.N.O., J.A.H.), University of Texas Southwestern Medical Center, Dallas, Tex.

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Correspondence to Joseph A. Hill, MD, PhD, Cardiology Division, Department of Internal Medicine, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-8573. E-mail joseph.hill@UTsouthwestern.edu

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Functional Effects of Preventing Hypertrophic Growth in the Setting of Pressure Overload

Species	Model	Intervention	Functional Response	Reference
Mouse	TAB	CsA	Normal LVSF and longevity	Hill et al[23]
Mouse	AAB	AT2 knockout	Normal LVSF	Senbonmatsu et al[137]
Rat	L-NAME-induced hypertension	L-NAME	Normal LVSF	Bartunek et al[138]
Mouse	AAB	Cardiac-specific overexpression of dn-CaN	Normal LVSF	Zou et al[26]
Mouse	Ang II infusion	AT2 knockout	Normal LVSF	Ichihara et al[139]
Mouse	AAB	Cardiac-specific overexpression of dn-gp130	Normal LVSF	Uozumi et al[140]
Mouse	TAB	Cardiac-specific MCIP1 overexpression	Normal LVSF and longevity	Hill et al[32]
Mouse	TAB	Cardiac-specific inhibition of $G_{\alpha q}$; β-hydroxylase knockout	Normal LVSF despite documented increases in wall stress	Esposito et al[42]
Mouse	TAB	Cardiac-specific GSK-3β overexpression	Normal LVSF and longevity	Antos et al[63]
Mouse	Ascending aortic banding	Rapamycin	Normal LVSF, transstenotic pressure gradients	Shioi et al[141]
Mouse	TAB	Cardiac-specific gp130 knockout	Heart failure	Hirota et al[142]
Mouse	TAB	Cardiac-specific RGS4 overexpression	Depressed LVSF, increased mortality	Rogers et al[143]
Mouse	AAB	Fas receptor knockout	Heart failure	Badorff et al[144]
Mouse	TAB	Melusin knockout	Depressed LVSF, cardiomyopathy	Brancaccio et al[106]

TAB indicates thoracic aortic banding; LVSF, left ventricular systolic function; AAB, abdominal aortic banding; AT2, angiotensin II type 2 receptor; L-NAME, N^G-nitro-L-arginine methyl ester; Ang II, angiotensin II; and dn-CaN, dominant-negative calcineurin.

Entries are listed chronologically by reported effect on circulatory performance.

been investigated as antihypertrophic targets and omit several important pathways, such as mitogen-activated protein kinase (reviewed in Sugden and Clerk[16]) or the Gp130/Stat3 (reviewed in Hoshijima and Chien[17]), in which interruption has not been studied carefully as a potential therapeutic strategy.

Ca^{2+}/Calcineurin/Nuclear Factor of Activated T Cells

Calcineurin is a protein phosphatase that dephosphorylates transcription factors of the NFAT (nuclear factor of activated T cells) family, which leads to their translocation to the nucleus to activate target genes. It is well established that activation of the calcineurin/NFAT pathway is sufficient for the development of cardiac hypertrophy and failure.[18] However, establishing whether calcineurin is necessary for this process has been more problematic. Controversy regarding this issue derives from conflicting results in studies in vivo using the calcineurin inhibitors cyclosporine A (CsA) and FK506 to treat various models of hypertrophy. Many studies have reported attenuation of hypertrophy by CsA and FK506 (reviewed in Frey and Olson[13] and Leinwand[19]). However, there have also been studies that reported no significant attenuation of hypertrophy in vivo. In humans, immunosuppressive therapy after solid-organ transplantation is associated with cardiac hypertrophy secondary to drug-induced hypertension and nephrotoxicity[20,21]; that CsA treatment does not suppress hypertrophic growth is not surprising given that much higher doses of CsA (or FK506) are required to suppress calcineurin activity in the heart relative to T cells.[22] In animal studies, differences in experimental methodology, including differences in timing and dosing of drug treatment, and differences in species and strain likely contribute to these apparent discrepancies. However, as outlined below, this controversy has been resolved by the use of more specific, endogenous calcineurin inhibitors.

These early hypertrophy-prevention studies provided an opportunity to test the long-held tenet that cardiac hypertrophy is a required compensatory response to hemodynamic stress. For the first time, hypertrophic growth could be abolished while the inciting stimulus, pressure stress, was maintained. Surprisingly, in animals in which hypertrophy was eliminated by calcineurin suppression, no evidence of hemodynamic compromise was observed, at least over a period of several weeks.[23] Despite persistent increases in wall stress as predicted by Laplace's law, ventricular size and systolic function (as suggested by a normal ejection fraction) were preserved, and the animals were clinically healthy with normal longevity (Table). Although it is presently unclear whether this lack of adverse effect would be sustained over long periods of time in larger mammals, these findings suggest that calcineurin-mediated hypertrophic growth may not be a required compensatory response, at least under conditions of moderate stress. In so doing, they raise the prospect that therapies could be developed to modulate the hypertrophic response to mitigate maladaptive aspects of the phenotype.

More recent studies have relied on endogenous inhibition of calcineurin by genetic means. Overexpression in cardiomyocytes of AKAP79 or Cain/Cabin, molecules that associate with the calcineurin catalytic subunit and inhibit activity, blunts both phenylephrine- and angiotensin II–induced hypertrophy.[24] These results were extended in vivo, where transgenic overexpression of Cain/Cabin resulted in attenuation of both pressure-overload and isoproterenol-induced cardiac hypertrophy.[25] Forced expression of a dominant-negative calcineurin mutant confers protection against hypertrophy and fibrosis after abdominal aortic constriction,[26] and targeted ablation of the calcineurin-Aβ gene blunts the hypertrophic response to hormonal or pressure stress.[27]

In contrast to AKAP70 and Cain/Cabin, members of a family of calcineurin-interacting proteins termed DSCR1/

MCIPs (modulatory calcineurin-interacting protein) are expressed at high levels in striated muscle and may function as endogenous modulators of calcineurin in the heart.[28–30] Cardiac overexpression of MCIP1 inhibited the progression to dilated cardiomyopathy in MCIP1/calcineurin double-transgenic mice.[31] Moreover, hypertrophic growth induced by isoproterenol, exercise, or thoracic aortic banding were all blunted in this model.[31,32] Recent data from mice with targeted deletion of MCIP1 suggest a dual role for MCIP1 in the regulation of calcineurin activity, *viz* low levels of MCIP1 expression may facilitate calcineurin signaling, but eventually MCIP1 must dissociate from calcineurin for full activation.[33]

Given that calcineurin-dependent signaling is involved in many, if not all, causes of cardiac hypertrophy, it is an attractive target for the prevention and treatment of hypertrophic heart disease. Mice that overexpress MCIP1 and are subjected to surgical pressure overload are clinically healthy despite significant blunting of the hypertrophic growth response.[32] Noninvasive and hemodynamic measures of cardiac performance are normal as late as 3 months, the latest time point examined. These findings confirm that cardiomyocyte-autonomous suppression of cardiac hypertrophy does not provoke hemodynamic collapse. However, it remains to be seen whether these data can be confirmed in studies with longer observation periods or in large animals. Moreover, the finding that exercise-induced cardiac hypertrophy is attenuated in MCIP1-transgenic hearts suggests that calcineurin plays a role in "physiological" hypertrophy as well. It is conceivable that a baseline level of calcineurin activity is required to prevent atrophy of the heart. For example, calcineurin-mediated NFAT activation is critical in preventing cardiomyocyte apoptosis.[34] Thus, a major challenge for the future will be to tailor calcineurin inhibition spatially and quantitatively to prevent the injurious sequelae of overactive calcineurin without provoking adverse effects on the physiological function of the heart (and other tissues).

G-Protein–Coupled Receptors

Myocardial G-protein–coupled receptors (GPCRs), including adrenergic, angiotensin, and endothelin (ET-1) receptors, serve a fundamental role in the regulation of cardiac function and hypertrophic growth,[35,36] and they are the site of action of numerous clinically useful drugs. GPCRs are coupled to 3 principal classes of heterotrimeric GTP-binding proteins, $G_{\alpha s}$, $G_{\alpha q}/G_{\alpha 11}$, and $G_{\alpha i}$, which transduce agonist-induced signals to intracellular effectors such as enzymes and ion channels.

Activation of $G_{\alpha q}$-coupled receptors is sufficient to induce hypertrophy in vitro and cardiomyopathy in vivo (reviewed in Adams et al[37] and Koch et al[38]). Combined genetic ablation of the $G_{\alpha q}$ and $G_{\alpha 11}$ genes results in embryonic lethality due to myocardial hypoplasia.[39] Cardiac-specific ablation of $G_{\alpha 11}/G_{\alpha q}$ in adult animals results in an almost complete lack of cardiac hypertrophy in response to aortic banding,[40] and overexpression of a dominant-negative mutant of $G_{\alpha q}$ in transgenic mouse hearts blunts pressure-overload hypertrophy.[41] Noteworthy is the fact that transgenic animals display a significantly slower pace of deterioration of systolic function than wild-type controls despite a documented lack of normalization of wall stress.[42] Similar findings were reported in mice lacking dopamine β-hydroxylase, the essential enzyme for the synthesis of norepinephrine.[42] Together, these findings lend further support to the hypothesis that cardiac hypertrophy is neither required nor necessarily adaptive, at least not in rodent models for up to 3 months (Table).

Cardiac overexpression of β_1-receptors, the most abundant adrenergic receptor in the heart, or $G_{\alpha s}$, its downstream effector, initially increases contractile function but eventually results in cardiomyocyte hypertrophy, fibrosis, and progressive deterioration of cardiac performance.[43–45] Interestingly, overexpression of β_2-receptors, which couple to both $G_{\alpha s}$ and $G_{\alpha i}$,[46] is detrimental only at excessive levels (>100-fold), whereas moderate levels of expression improve basal contractile function and rescue the cardiomyopathic phenotype of $G_{\alpha q}$-transgenic mice.[47] Inhibition of β-adrenergic receptor kinase (βARK), a kinase involved in receptor desensitization, by overexpression of the inhibitory peptide βARKct attenuates cardiomyopathy secondary to deficiency of the sarcomeric protein MLP.[48] Moreover, βARKct overexpression significantly blunts the development of cardiac hypertrophy and delays development of systolic dysfunction in calsequestrin transgenic mice, which again demonstrates the beneficial effects of inhibition of cardiac hypertrophy.[49]

Phosphoinositide 3-Kinase/Akt/Glycogen Synthase Kinase-3

Phosphoinositide 3-kinases (PI3Ks) have been implicated in the regulation of many cellular functions, including cell growth, survival, and proliferation.[50] Overexpression of a constitutively active PI3K (p110α) mutant in the heart leads to increased heart size; conversely, hearts expressing a dominant-negative PI3K are small.[51] Interestingly, cardiac function under resting conditions was not perturbed in either model but declined in dominant-negative PI3K mice subjected to pressure overload but not in exercise-trained animals.[52] One study demonstrated that pathways for hypertrophic growth and contractile function can be dissociated in vivo: p110α-dependent signaling mediates cardiomyocyte hypertrophy, whereas p110γ negatively regulates contractile function by inhibiting cAMP production without affecting cardiomyocyte size.[53]

An important target of PI3K signaling is the serine/threonine kinase Akt (also known as protein kinase B). Overexpression of Akt is sufficient to induce cardiac hypertrophy in transgenic mice without adverse effects on systolic function.[54,55] Akt regulates at least 2 downstream targets in hypertrophic signaling, the mammalian target of rapamycin (mTor) and glycogen synthase kinase (GSK)-3. mTor activates key regulators of protein translation such as p70S6 kinase and 4EBP1/eIF4E, thereby enhancing protein synthesis, a classic feature of cardiomyocyte hypertrophy. Binding of the immunosuppressive drug rapamycin coupled to its intracellular receptor FKBP12 inhibits the activity of mTor. Rapamycin, a compound used successfully to treat transplant rejection in clinical practice, is able to attenuate cardiac hypertrophy secondary to constitutive activation of Akt[56] or a variety of hypertrophic stimuli.[57–60]

Akt phosphorylates and thereby inhibits GSK-3β, a widely expressed kinase that phosphorylates transcription factors of

the NFAT family, promoting translocation to the cytoplasm, where they are inactive. The β-adrenergic agonist isoproterenol[61] and both endothelin-1 (ET-1) and phenylephrine[62] induce GSK-3β phosphorylation in a PI3K-dependent fashion, which indicates that inactivation of GSK-3β might be required for hypertrophic growth. In fact, expression of a phosphorylation-resistant mutant of GSK-3β results in inhibition of ET-1–mediated hypertrophy in vitro.[62] Similarly, transgenic overexpression of this GSK-3β mutant in mouse hearts significantly decreases hypertrophy in response to chronic isoproterenol administration and pressure overload.[63] Of note, several other transcription factors implicated in the hypertrophic response are phosphorylated by GSK-3β, including GATA4.[64]

Activation of GSK-3β results in enhanced expression of atrial natriuretic peptide (ANP), while at the same time suppressing other genes in the "hypertrophic program."[61,63] Activation of ANP-dependent signaling or its downstream mediators (guanylyl cyclase-A receptor, protein kinase G) evokes potent antihypertrophic effects in vitro and in vivo.[65–68] It is tempting to speculate that the ability of GSK-3 to uncouple ANP expression from the fetal gene program contributes to its hypertrophy-suppressing properties.

Taken together, these findings support the notion that GSK-3 integrates signals of multiple hypertrophic pathways and that GSK-3 inactivation is required for the development of many forms of cardiac hypertrophy. Given this, GSK-3 is an attractive target for therapeutic intervention. However, the pleiotropic actions of GSK-3 in multiple tissues pose significant challenges, and a great deal more work is required.

Myocyte Enhancer Factor-2/Histone Deacetylases

Because several hypertrophic pathways are capable of evoking similar morphological and molecular phenotypes, it is plausible that these signaling cascades converge on common downstream targets. A candidate in this regard is MEF2 (myocyte enhancer factor-2). MEF2 proteins display only basal levels of transcriptional activity and become active only on upstream stimulation, thus fulfilling criteria for a potential integrator of "pathological" growth signals. Accordingly, transgenic expression of a dominant-negative mutant of MEF2 in mouse hearts results in impaired cardiac growth.[69]

MEF2 activity is regulated by direct association with histone acetylases (HATs) and deacetylases (HDACs; reviewed in McKinsey et al[70]). These chromatin remodeling enzymes are recruited to target genes by binding to specific transcription factors such as MEF2. HATs acetylate nucleosomal histones, promoting chromatin relaxation and transcriptional activation, and HDACs antagonize this function. Phosphorylation of class II HDACs by CaMK and other kinases disrupts their tight association with MEF2, which results in derepression of transcriptional activity and nuclear export of HDAC molecules. Accordingly, HDACs have been shown to inhibit hypertrophic signaling, serving as a "brake" on the myocardial growth response[71] (Data Supplement Figure).

Mutant class II HDACs that lack regulatory phosphorylation sites render cardiomyocytes resistant to serum- or phenylephrine-induced hypertrophy and fetal gene activation. Mice that lack HDAC9 exhibit normal cardiac size and function at an early age but manifest an exaggerated response to thoracic aortic banding and calcineurin activation, which is accompanied by superinduction of "hypertrophic genes."[71] Conversely, very recent results suggest that expression of antihypertrophic genes in the heart is inhibited by HDAC2, a class I HDAC.[72] Thus, HDAC-mediated chromatin remodeling may regulate a relative balance between prohypertrophic and antihypertrophic transcriptional processes, opening new possibilities in the prevention and treatment of cardiac hypertrophy and failure. In general, regulation of transcriptional activity by chromatin structure and function is likely to emerge as a novel target for therapy.

Peroxisome Proliferator-Activated Receptors

Energy metabolism in the adult myocardium depends largely on mitochondrial oxidation of long-chain fatty acids. Cardiac hypertrophy is associated with suppression of fatty acid oxidation and metabolic reversion to increased glucose utilization, which is characteristic of the fetal heart (reviewed in Lehman and Kelly[73]). This shift could be viewed as an adaptive response, because it decreases oxygen consumption per mole of ATP generated. However, maladaptive features exist, including increased lipid accumulation in the heart stemming from chronically impaired oxidation of fatty acids,[74] lactic acid accumulation, and diminished maximal ATP generation from glycolysis.

Genes involved in fatty acid oxidation are regulated by the peroxisome proliferator-activated receptor (PPAR) family of transcription factors. The 3 PPAR isoforms, α, β/δ, and γ, belong to a superfamily of nuclear hormone receptors and are activated by diverse ligands, including unsaturated fatty acids and isoform-specific drugs such as fibrates (PPARα) and antidiabetic drugs of the thiazolidinedione class (PPARγ). These latter agents attenuate angiotensin II–induced hypertrophic gene expression, as well as increases in cardiomyocyte size in vitro.[75,76] Heterozygous PPARγ-deficient mice display an exaggerated hypertrophic response to aortic banding, whereas the PPARγ agonist pioglitazone significantly blunts myocardial hypertrophy in banded wild-type mice.[75]

PPARα, the predominant PPAR isoform in the heart, has been implicated in hypertrophic signaling. PPARα expression is significantly diminished during pressure-overload hypertrophy, along with several other key enzymes of lipid metabolism.[77] Some evidence suggests that PPARα downregulation is an adaptive response: agonist-induced PPARα activation leads to contractile dysfunction in rat hearts subjected to pressure overload,[78] and cardiac overexpression of PPARα leads to cardiomyopathy with contractile dysfunction.[79] Genetically engineered mice lacking the PPARα gene were protected from diabetes-induced cardiac hypertrophy and dysfunction.[80] Intriguingly, a single-nucleotide polymorphism within intron 7 of the PPARα gene independently predicted the degree of ventricular hypertrophy due to exercise in healthy volunteers.[81] The significance of cardiac energy metabolism in the development and progression of myocardial hypertrophy is further highlighted by the recent finding that MEF2 and HDAC5 regulate the expression of

PGC-1 (PPARγ coactivator-1), a master regulator of mitochondrial biogenesis and fatty acid oxidation.[82]

Small G Proteins

Small G proteins play an important role in sarcomeric and cytoskeletal organization, hallmark features of the hypertrophic phenotype. Small G proteins also regulate such diverse processes as cell growth, division and survival, membrane trafficking, and cellular motility (reviewed in Clerk and Sugden[83]). Several small GTPases have been implicated in hypertrophy and studied as therapeutic targets.

Ras, the first small G protein shown to be involved in cardiac hypertrophy, induces a significant increase in cardiac mass when a constitutively active mutant is overexpressed in transgenic mouse hearts.[84] Likewise, expression of this Ras mutant in neonatal rat cardiomyocytes results in hypertrophic gene expression,[85] whereas dominant-negative Ras mutants blunt phenylephrine-mediated increases in cell size and protein synthesis.[86,87]

The Rho family of small G proteins, consisting of RhoA, Rac, and Cdc42 subfamilies, regulates cytoskeletal organization in cardiomyocytes.[88] RhoA activates several protein kinases, specifically Rho-associated kinase (ROCK), and potentiates GATA4 transcriptional activity to induce a hypertrophic phenotype in neonatal rat cardiomyocytes.[89] Dominant-negative RhoA mutants, as well as inhibitors of ROCK, prevent cardiomyocyte hypertrophy in vitro.[90] However, overexpression of RhoA in transgenic mouse hearts is not sufficient to induce ventricular hypertrophy but rather leads to cardiac conduction abnormalities with bradycardia and ultimately a dilated phenotype and heart failure.[91]

Constitutive activation of Rac in cardiomyocytes in vitro[92] and in vivo[93] leads to hypertrophy associated with alterations in focal adhesions, whereas a dominant-negative Rac mutant prevents phenylephrine-induced increases in protein synthesis and cardiomyocyte size. Likewise, a dominant-negative focal adhesion kinase (FAK) attenuates the hypertrophic phenotype, as well as the induction of ANP expression, after either ET-1[94] or phenylephrine[95] stimulation.

Signal transduction by small G proteins requires covalent attachment of isoprenoid intermediates (isoprenylation), which in turn leads to membrane targeting. Cholesterol-lowering drugs of the statin class (HMG-CoA reductase inhibitors) block formation of isoprenoid intermediates, thereby inhibiting small G protein function. Accordingly, both angiotensin II–induced[96] and phenylephrine-induced[97] cardiomyocyte hypertrophy are prevented by statin treatment in vitro. Simvastatin significantly reduces hypertrophy in rats with pressure overload due to aortic banding.[98] Likewise, the hypertrophic and cardiomyopathic phenotype of a double-transgenic rat with overexpression of both renin and angiotensinogen is improved by cerivastatin treatment.[99] Fluvastatin increases survival in a murine model of myocardial infarction.[100] This effect is associated with attenuation of left ventricular dilation and lower end-diastolic pressures, which suggests a favorable effect on postinfarction ventricular remodeling. Patel et al[101] demonstrated regression of myocardial hypertrophy and fibrosis in transgenic rabbits overexpressing a β-MHC mutation after treatment with simvastatin. In fact, simvastatin inhibits cardiac hypertrophy due to aortic banding while simultaneously preventing Rho-geranylgeranylation.[102] Statins inhibit hypertrophy in spontaneously hypertensive rats, accompanied by a decrease in the GTP-binding activity of Rac1 and RhoA.[103] Although it is clear that prevention of acute vascular events underlies most of the substantial clinical benefit afforded by these drugs, it is tempting to speculate that suppression of myocyte small G-protein signaling plays some role.

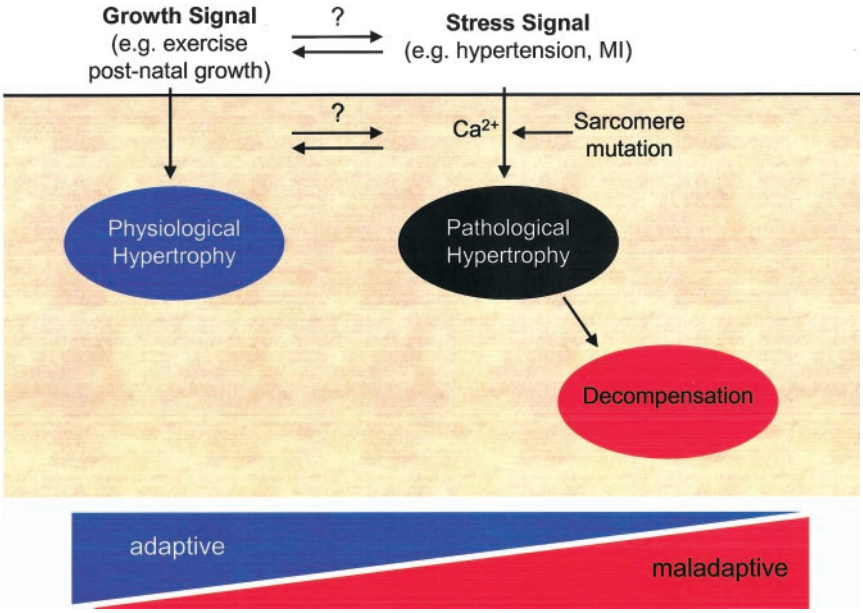
Biomechanical Sensors in Hypertrophic Signaling

Mechanical stress induced by physical stretching of neonatal or adult cardiomyocytes is sufficient to induce hypertrophic gene expression and a hypertrophic phenotype, notably in the absence of humoral or neuronal factors (reviewed in Sadoshima and Izumo[104]), which suggests a cell-autonomous mechanism. Mechanical stress induces a number of growth responses, including activation of several hypertrophic signaling cascades, increases in protein synthesis, and release of vasoactive peptides (reviewed in Zou et al[105]). As noted earlier, different types of biomechanical stimuli, such as pressure or volume, induce distinct molecular responses. Despite the pathophysiological importance of biomechanical stress–induced growth responses, and their potential candidacy for therapy, little is known about how biomechanical stress is sensed by the cardiomyocyte and transduced into prohypertrophic intracellular signals.

Several potential mediators of "mechanosensing" have been proposed, including stretch-activated ion channels and integrins. Mice lacking melusin, a protein that interacts with β_1-integrin at the costamere, fail to mount a significant hypertrophic response to pressure stress but rather display a dilated phenotype with severely depressed cardiac function.[106] In contrast, administration of subpressor doses of angiotensin II or phenylephrine in these mice leads to cardiac hypertrophy indistinguishable from wild-type mice, which suggests a specific role for melusin in the transmission of biomechanical stress. Other data suggest that mechanotransduction may occur at the sarcomeric Z disk. Cardiomyocytes derived from mice lacking the Z-disc protein MLP (muscle LIM protein) selectively fail to respond to stretch, whereas the response to $G_{\alpha q}$-coupled agonists is not compromised.[107] Moreover, a human mutation within the *MLP* gene that disrupts telethonin/T-cap binding leads to dilated cardiomyopathy.[107] We recently identified a new family of striated muscle-specific Z-disc proteins, termed calsarcins, which interact with both telethonin/T-cap and calcineurin,[108] which suggests a possible role in linking mechanosensation to hypertrophic signaling.

Na/H Exchanger

Cardiac Na^+/H^+-exchanger (NHE) activity is upregulated in several in vivo and in vitro models of cardiac hypertrophy.[109,110] Elevated NHE activity depletes the transmembrane Na^+ gradient, which leads to increased intracellular Ca^{2+} mediated by the Na/Ca-exchanger (reviewed in Cingolani and de Hurtado[111]) and consequent activation of several signaling cascades (reviewed in Frey and Olson[13]). Accordingly, inhibition of NHE by its specific inhibitor cariporide has been demonstrated to "rescue" several models of cardiac hypertrophy in vivo.[111–113] Because NHE inhibition does not appear to



Physiological hypertrophy is an adaptive response to growth signals. Pathological hypertrophy develops in response to stress signals. It is not known whether stress signals are unique or whether overstimulation ("too much of a good thing") evokes a pathological response. Similarly, it is not known whether physiological versus pathological hypertrophy derives from activation of unique, "beneficial" signaling cascades or whether extreme activation of these same pathways evokes a pathological response. MI indicates myocardial infarction.

be associated with adverse hemodynamic consequences, this approach is a potentially interesting antihypertrophic treatment option.

Ca^{2+} Cycling

Considerable attention has been focused on abnormalities of Ca^{2+} cycling in hypertrophy as a possible therapeutic target. In heart failure, diminished systolic Ca^{2+} transients derive, at least in part, from depletion of Ca^{2+} stores. This depletion, in turn, stems from the synergistic actions of (1) adrenergic activation, (2) decreased expression of the sarcoplasmic reticulum Ca^{2+} pump SERCA2a, and (3) hypophosphorylation of phospholamban, which augments the tonic inhibitory action of phospholamban on SERCA2a. Exciting therapeutic approaches have been directed at restoring sarcoplasmic reticulum Ca^{2+} stores, either by decreasing β-adrenergic receptor activity,[114] overexpressing SERCA2a[115,116] or the Ca^{2+}-binding protein S100A1,[117] or eliminating phospholamban.[118,119] Indeed, the cardiomyopathic phenotype in several[120–123] but not all[124] genetic models can be rescued by targeted deletion of phospholamban. Recent reports, however, have described missense[125] or nonsense[126] mutations in phospholamban in familial pedigrees of dilated cardiomyopathy, which highlights the challenges that lie ahead in envisioning Ca^{2+} cycling as a therapeutic target.

Physiological Versus Pathological Hypertrophy

In some instances, such as in endurance athletes, cardiac hypertrophy is generally accepted to be physiological and not associated with adverse sequelae. Little is known, however, about the specific molecular events that lead to physiological hypertrophy and how these pathways differ from pathological hypertrophy. The morphological phenotypes differ significantly: Exercise-induced hypertrophy is typically not accompanied by myocardial accumulation of collagen, and increases in wall thickness are modest. Scheuer and coworkers[127] demonstrated that physiological and pathological hypertrophy differ in their respective myosin isoform compositions and that the predominance of myosin V3 expression in hypertensive rats could be reversed by chronic exercise. Spontaneously hypertensive rats express higher levels of "hypertrophic genes," such as brain natriuretic peptide or ET-1, compared with exercised rats, despite similar degrees of left ventricular hypertrophy.[128] Transcriptional profiling of exercised rat hearts demonstrated down-regulation of hypertrophic "markers."[129] Similarly, both thyroid hormone receptor expression and α/β-MHC isoform expression are regulated in opposite directions in exercise-induced hypertrophy compared with that induced by pressure overload.[130] Pressure and volume stress induce distinct molecular responses; despite a similar degree of hypertrophy and ANP induction, marked differences in the expression levels of β-myosin, α-skeletal actin, and SERCA2a were observed in pressure overload–induced hypertrophy relative to volume overload.[131]

Taken together, hypertrophic signaling can be viewed as a web that integrates and modulates a multitude of input signals (Figure). Whereas multiple endogenous and exogenous inhibitors of cardiac hypertrophy have been identified, it will be critical to specifically target "pathological" hypertrophy while preserving the heart's ability to adapt to an increase in physiological demands. Some evidence suggests this may be possible.

Evidence From Clinical Trials

Most modern treatments of heart failure, including β-blockers and ACE inhibitors, aim to delay or even reverse the maladaptive remodeling process, and there is a great deal of evidence to support their use in patients with structural heart disease. It is difficult, however, to derive mechanistic insights from many clinical studies, because the beneficial impact of energy-sparing therapies (eg, afterload reduction, heart rate lowering) is confounding. Recent trials comparing treatments with similar blood pressure–lowering effects suggest that interruption of hypertrophic signaling pathways may confer differing degrees of clinical benefit. In the Losartan Interven-

tion For Endpoint reduction in hypertension (LIFE) trial, 9139 patients with hypertension and ECG-documented left ventricular hypertrophy were randomized to receive either the AT1 receptor blocker losartan or the β_1-receptor blocker atenolol. Whereas the blood pressure–lowering effects were similar, patients taking losartan displayed significantly less hypertrophy and were less likely (relative risk 0.87, $P=0.02$) to suffer a major cardiovascular event.[132] In the Heart Outcomes Prevention Evaluation (HOPE) trial, the ACE inhibitor ramipril afforded significant clinical benefit[133] and decreased the development (and caused regression) of hypertrophy[134] independently of its blood pressure–lowering effects. In contrast, persistence of cardiac hypertrophy (despite similar blood pressure changes) predicted an adverse outcome. Together, these findings are consistent with results from animal models, which suggests that angiotensin ($G_{\alpha q/\alpha 11}$) signaling may induce a maladaptive form of hypertrophy that can be suppressed to provide clinical benefit. The recent Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) has generated considerable debate, but its findings have been used to argue against α-adrenergic blockade as a primary mean of blood pressure lowering.[135,136]

Caveats

Detailed dissection of hypertrophic signaling raises the prospect of enhancing the desirable features of hypertrophy (eg, increased sarcomere organization) while inhibiting maladaptive features (eg, decompensation, arrhythmogenesis, and contractile isoform switching). Several caveats pertain. Reports demonstrating benefit from inhibition of cardiac hypertrophy despite persistence of the initiating stimulus have been short term (≈10% to 15% of a normal mouse lifespan); long-term targeting of hypertrophy in a heart with increased wall stress might still result in failure. In addition, certain hypertrophic signaling pathways may need to be basally active to prevent myocyte atrophy. Thus, strategies for suppressing excessive activation of such pathways may need to be titrated precisely to avoid disruption of cardiac homeostatic mechanisms. Finally, studies to date have focused on caged rodents with short life spans, and work using large animal models is required.

Summary

Taken together, these data suggest that hypertrophy may be a valid, independent target for therapeutic intervention in selected patients. However, it remains to be seen whether hypertrophy induced by diverse forms of stress responds similarly to interruption of these pathways. Moreover, because of the pleiotropic actions of drugs used in some of these studies, it is unclear whether novel therapies that selectively target mediators of hypertrophic signaling also confer clinical benefits.

Recent discoveries demonstrating that the “compensatory” role of cardiac hypertrophy is not universally required may have uncovered a chink in the armor of hypertrophy. Major challenges remain to dissect mechanisms underlying the maladaptive features of hypertrophy, but patients with heart disease are likely to benefit from these efforts.

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