Decompensation of Cardiac Hypertrophy: Cellular Mechanisms and Novel Therapeutic Targets

Cardiac hypertrophy leads to heart failure, and both conditions can ultimately prove lethal. Here, traditional and novel mechanisms relating hypertrophy and heart failure are described at the physiological, cellular, and molecular levels. The rational application of these mechanistic considerations to therapeutics targeting hypertrophy and heart failure is discussed.

**Basic Concepts of Compensatory and Decompensated Cardiac Hypertrophy**

Hypertrophy [from the Greek hyper (over) and trophy (growth)] of the human heart is a morphological clinical diagnosis defined by increased myocardial mass. Premortem, the diagnosis is usually based on calculated echocardiographic or magnetic resonance imaging estimates of left ventricular mass. Postmortem, the pathological diagnosis is based on direct measurements of gravimetric heart weight. Notably, there is no functional aspect to the diagnosis of cardiac hypertrophy, and it can occur in hearts with normal, supernormal, or depressed cardiac performance. Thus “hypertrophy” per se does not necessarily imply disease, since conditioned athletes can develop cardiac enlargement and increased myocardial mass with no adverse consequences. This exercise-induced or “physiological” hypertrophy is distinguished from pathological stress-induced hypertrophy at the molecular, cellular, functional, and prognostic levels (22) and, except where specifically stated, is not the topic of this review.

Determining whether cardiac hypertrophy exists in individual patients is a medical imperative because of irrefutable epidemiological evidence that it constitutes an important independent risk factor for death (41, 49, 80). The same studies also indicate that cardiac hypertrophy with normal cardiac function tends to progress over time to depressed cardiac function, described as “hypertrophy decompensation,” and clinically resulting in the syndrome of heart failure (broadly defined as any condition in which the forward output of the heart is insufficient to meet the metabolic demands of the organism). Heart failure itself is a highly lethal disease with a 5 year mortality in treated patients that is worse than that of many malignancies (38) and that affects 5 million adults in the United States alone. Thus the human suffering and societal burden of heart failure is staggering (79), and the possibility that prevention of hypertrophy decompensation could reduce the prevalence of heart failure has provided a strong impetus for mechanistic studies of the decompensation process and prompted attempts to develop potential means of preventing hypertrophy or its pathological sequelae. Indeed, primary or secondary prevention of hypertrophy, as with treatment of hypertension using vasodilators or neurohormonal inhibitors, can improve clinical outcomes (57).

At the cellular level, cardiac hypertrophy is the consequence of an increase in cardiac myocyte size. Since cardiac myocytes have little or no capacity for cellular proliferation, their only means of growth is by cellular enlargement. Since cardiac failure most commonly results from an insufficiency of myocardium (as opposed to an abnormal increase in metabolic demand, as in “high output failure”), it is not surprising that cardiomyocyte hypertrophy is the dominant cellular response to virtually all forms of hemodynamic overload or myocardial injury. Although it seems intuitively obvious that growing more myocardium could produce functional adaptation in a syndrome caused by myocardial insufficiency, specific hemodynamic benefits can be demonstrated through application of physical principles in the context of known biological events. These principles explain hypertrophic compensation as an adaptive mechanism that preserves cardiac ejection performance by normalizing wall stress (FIGURE 1). The Laplace relationship establishes that wall stress (which at ventricular end systole can be considered as cardiac “afterload”) of a thin-walled sphere is determined by intraluminal pressure, chamber size, and wall thickness:

$$\sigma = pr/2h$$

where $\sigma$ is wall stress, $p$ is intracavitary pressure, $r$ is the internal radius of the chamber, and $h$ is the thickness of the chamber walls. Thus, in a situation such as hypertension where increased pressure results in increased stress on the heart, a reactive increase in wall thickness (FIGURE 1, $h'$) can normalize wall stress and preserve systolic function (29). This is the basis for previous designations of reactive cardiac hypertrophy as “compensatory.” However, as...
discussed below, recent studies in which pressure overload hypertrophy has been inhibited through genetic modification of hypertrophy signaling pathways suggest that “compensatory” hypertrophy may not actually be essential to functional compensation, at least in the short term (24, 34, 35, 71).

Long-term maladaptive remodeling of reactive hypertrophy is associated with progressive ventricular dilation. The consequences of cardiac enlargement ($r'$) and wall thinning ($h''$) on wall stress are also shown in Figure 1: When the ratio $r'/h''$ increases, so does wall stress, despite constant intracavitary pressure. This geometrical increase in wall stress generates its own hemodynamic stress on the heart, further stimulating already overloaded hypertrophy signaling pathways and tipping the balance from a cell growth response to one of cell death. Once these processes have progressed to this stage, i.e., decompensation, loss of cardiac myocytes and their replacement by fibrous tissue rapidly diminishes contractile performance in “end-stage” cardiomyopathy, leading to irreversible functional deterioration, intractable heart failure, and ultimately death.

**Cardiac Myocyte Death: A Cause and Consequence of Hypertrophy Decompensation**

Although stress-mediated myocardial hypertrophy is a complex condition associated with numerous adverse consequences, including alterations in intercellular matrix leading to interstitial fibrosis, loss of β-adrenergic receptor responsiveness, and metabolically unfavorable changes in contractile protein isoforms, the defining irreversible cellular event in hypertrophy decompensation is cardiomyocyte degeneration and death, detected histologically in early cardiomyopathy as “cardiomyocyte drop-out.” It is a biological irony that the same neurohormones that stimulate “compensatory” cardiomyocyte hypertrophy in response to hemodynamic stress also contribute to cell death (2, 20, 21). Whereas the exact pathway to cell death varies with physiological context, there are three clearly defined pathologically and mechanistically distinct modes of death: necrosis (oncosis), apoptosis, and autophagy (54) (Figure 2). There is clinico-pathological evidence for all three forms of death in end-stage human cardiomyopathy (33, 72). Thus cardiomyocyte replacement and myocardial fibrosis are characteristic of all forms of pathological hypertrophy and progress in parallel with functional decompensation (33, 45, 72). Presaging actual cardiac myocyte death is ultrastructural evidence of myocyte degeneration with loss of sarcomeric organization and an increase in cytoskeletal elements in terminal failing human left ventricular myocardium. Likewise, progressive left ventricular remodeling in severe aortic valvular stenosis exhibits myocyte degeneration and fibrosis that correlates with worsening systolic function (33).

![Figure 1](http://physiologyonline.physiology.org/)

**Figure 1. Development and progression of decompensated chamber hypertrophy**

Compensated cardiac hypertrophy manifests as an increase in ventricular wall thickness ($h'' > h$, wall thickness), characterized by cardiomyocyte growth in response to hemodynamic stress and/or myocardial injury. Neurohormonal activation transduces development of hypertrophy. Cardiomyocyte death provokes transition to cardiomyopathic dilation ($r' > r$, radius of the ventricular cavity) and wall thinning ($h'' < h'$). Inset: the inverse relationship between ventricular wall stress and contractile performance, with progression of compensated hypertrophy to cardiomyopathic decompensation.
this study, morphological evidence for all three cell death pathways (oncosis or necrosis, apoptosis, and autophagy) was seen in hypertrophied myocardium with worsening ventricular systolic function, i.e., during the decompensation phase.

Cardiomyocyte Necrosis in Decompensated Heart Failure: A Stake Through the Heart

Oncosis (from the Greek onkos for mass or tumor) was a term coined by Von-Recklinghausen to describe the characteristic cellular swelling and karyolysis observed in some forms of cellular death. Subsequent studies identified oncosis as a form of ischemic necrosis (from nekros, Greek for dead body) in various model systems (54, 89). Cardiac myocyte necrosis is the oldest postulated means of cell death in decompensating hypertrophy leading to cardiomyopathy, and an intriguing mechanistic hypothesis was developed to causally link cardiomyocyte hypertrophy and death: the “ischemic core” hypothesis. The notion is that hypertrophy, which in human heart failure can increase cardiomyocyte cross-sectional area threefold, simply overwhelms the physiological and physical limits of oxygen delivery to the center of the myocyte. Oxygen diffusion through cell cytoplasm (largely water) is invariant, as is the physiological range of oxygen tension that forms the diffusion gradient through the cell. Thus, when the cross-sectional area of a cardiac myocyte exceeds the distance across which oxygen can diffuse down its concentration gradient from adjacent capillaries, mitochondria at the core of the cardiomyocyte become ischemic, with resulting diminished ATP-generating ability and contractile depression (81). Additionally, cardiac hypertrophy is associated with a relative decrease in myocardial capillary density because capillary angiogenesis does not occur in parallel with hypertrophying myocytes (37), resulting in an absolute reduction in myocardial oxygen delivery per unit of myocardium. Finally, perivascular and interstitial fibrosis produce a physical diffusion barrier for delivery of nutrients and oxygen.

The necrotic core mechanism is intellectually appealing but has been difficult to prove. Supportive evidence has been generated in a murine model of inducible activated Akt/protein kinase B (74). The Akt-signaling pathway is an important mediator of non-pathological (“physiological”) myocardial growth, as induced by growth factor pathways and exercise (21). However, sustained activation of Akt signaling through forced expression of myristoylated (activated) AKT provoked progressive left ventricular dilation with systolic dysfunction, i.e., the development of dilated cardiomyopathy and heart failure (58). Development of cardiomyopathy should not have occurred if Akt-induced hypertrophy is physiological, unless the hypertrophy itself causes secondary pathology. Recently, conditional myocardial expression of activated Akt caused reversible hypertrophy at 2 weeks but a progressive and irreversible cardiomyopathy with decreased myocardial capillary density and increased fibrosis after 6 weeks (74). Notably, coronary angiogenesis was enhanced during the compensated acute hypertrophic phase but was reduced during the period of pathological remodeling and hypertrophy decompensation. Additionally, inhibition of angiogenesis using a decoy VEGF receptor in the acute phase led to decreased capillary density, contractile dysfunction, and impaired cardiac growth. The association of decreased vascularity and progression to decompensated cardiomyopathy in a model of excessive “physiological” hypertrophy supports the necrotic core hypothesis. The converse experiment, determining whether enhanced angiogenesis can ameliorate the transition of compensated to decompensated hypertrophy, has not yet been reported.

Apoptosis in Hypertrophy Decompensation: Suicide is not Painless

Although necrosis is cell death caused by intrinsic factors, cells can also choose suicide via inducible cell
death programs. The most completely studied form of programmed cell death in heart failure is apoptosis (from the Greek apo, meaning away from, and ptosis, meaning falling), a term originally used to describe the series of programmed death events that culminates in the autumnal falling of leaves from deciduous trees. There are numerous examples of clinical cardiomyopathies and experimental models of heart failure or hypertrophy decompensation in which apoptosis is strikingly increased and likely plays a significant pathophysiological role (5, 10, 23, 26, 50, 62, 64, 82).

Apoptosis is a generalized but highly regulated cell response that is essential to eliminate unnecessary tissue that develops during embryonic differentiation (such as the regression of inter-digital webs of the hands) (52) and that limits the proliferation of abnormal or damaged cells that could otherwise form malignant tumors (83). Cells undergoing apoptosis are distinguished morphologically from oncosis and other forms of cell death by characteristic nuclear chromatin condensation and nuclear fragmentation that forms dense “apoptotic bodies” (56). This process of protein and chromatin fragmentation into small packages that can be engulfed by scavenger cells provides for elimination of a dying cell without provocation of a potentially injurious inflammatory response. Thus apoptosis under normal conditions is a cleaner way of eliminating non-desirable cells and avoids or preempts cellular swelling, rupture, and secondary infiltration of inflammatory cells that occur with necrotic cell death.

As is proper for a tissue without any significant capacity for regeneration (12, 65), apoptosis is extremely rare in the normal myocardium, with reported rates of 1 apoptotic cardiomyocyte in 10,000–100,000 (75). However, the rate of cardiac myocyte apoptosis can increase by orders of magnitude in the human heart diseases associated with cardiomyocyte drop-out, such as dilated and ischemic cardiomyopathies (62, 64), hypertrophic heart disease (33), and arrhythmogenic right ventricular dysplasia (55). There are two distinct apoptosis signaling pathways that can be induced in heart failure: the death receptor and mitochondrial pathways. The general mechanisms of cardiac myocyte apoptosis have been the subject of many excellent reviews (14, 26, 53) and, therefore, are only summarized here. Briefly, in the death receptor pathway (also known as the extrinsic pathway), cell death is initiated by cytokine binding to membrane receptors, such as TNF superfamily receptors or Fas. Activated receptors oligomerize and form a death signaling complex containing FADD (Fas associated death domain-containing protein), which recruits caspase 8 and initiates the apoptotic cascade of caspase proteases that culminates in systematic degradation of intracellular proteins and oligonucleosomal DNA cleavage. In contrast, the mitochondrial pathway (also known as the intrinsic pathway) is initiated when outer mitochondrial membrane permeabilization permits cytochrome c release into the cytoplasm, resulting in formation of the apoptosome complex with Apaf-1, which recruits caspase 9 and initiates the caspase cascade.

Molecular links between hypertrophic and apoptotic pathways have been described for both the death receptor and the mitochondrial pathways. In the death receptor pathway, there are cyto-protective anti-apoptotic factors that antagonize the death receptor response. Ablation of one such protective “life receptor,” that for the cytokine signal transducer of interleukin-6 family proteins, Gp130, had no effects on normal cardiac function but caused a dilated cardiomyopathy and massive cardiac myocyte apoptosis after induction of pressure overload by acute microsurgical transverse aortic coarctation in mice (36). This striking result revealed the potentially catastrophic consequences when absence of a critical prosurvival pathway leads to disinhibition of cardiomyocyte apoptosis during development of pressure overload hypertrophy. Absence of a phenotype in nonstressed mice also indicates that cardiomyocyte apoptosis is somehow stimulated in cardiac myocytes by the hypertrophic process, which supports the notion that an apoptosis gene program is induced by cardiac hypertrophy.

Inducible pro-apoptotic genes have been detected in pressure overload hypertrophy of mice and humans (86) as well as in genetic mouse models of hypertrophy (6). In particular, details are emerging supporting a prominent role for the BH3-only, Bcl2 family protein, Nix, as a mediator of apoptotic hypertrophy decompensation. When transgenic expression of the Gq signaling protein, which transduces signals from epinephrine, angiotensin II, and endothelin receptors (20), was used to produce a model of reactive hypertrophy independent of hemodynamic overload, pathological hypertrophy developed (16) with provokable apoptosis in response to various forms of physiological stress (2, 70). In this model, cardiomyocyte apoptosis is unambiguously the cause of transitioning from compensated hypertrophy to decompensated heart failure, as inhibition of apoptosis by pharmacological caspase inhibition prevents cardiomyopathic degeneration (32). Transcriptome analysis of Gq hearts revealed several components of a putative inducible cardiomyocyte death program and led to identification of the Bcl-2 family member, Nix.

The Bcl-2 family proteins are a broadly expressed and evolutionarily conserved group of apoptosis modulators (1). Based on structural features, they are separated into “multidomain” and “BH3-only” classes. The multidomain proapoptotic Bcl-2 proteins, Bax and Bak, are

“Cardiac myocyte necrosis is the oldest postulated means of cell death in decompensating hypertrophy leading to cardiomyopathy...”
the essential pore-forming proteins that lead to mitochondrial outer membrane permeabilization and induction of the intrinsic apoptosis signaling cascade. Their many antiapoptotic counterparts, including prototypical Bcl2 and Bcl-xl, inhibit this process by heterodimerizing with their pro-apoptotic relatives. In contrast to the multi-domain proteins, the principal role of the subclass of BH3 domain-only proteins appears to be to regulate the multidomain proteins by sensing stress signals and undergoing increased expression, activation, or mitochondrial translocation (76). Thus the multidomain proteins are the effectors, and the BH3-only proteins the sensors and regulators, of mitochondrial pathway apoptosis. Nix, an inducible cardiac-expressed BH3-only protein, is transcriptionally upregulated in hypertrophies resulting from forced increases in Geq signaling, experimental pressure overload hypertrophy, and human hypertensive heart disease (86). Analysis of the transcriptional events leading to Nix induction has revealed an important role for PKC (28), which is activated in reactive hypertrophy (21). Transgenic overexpression of Nix was sufficient to produce an apoptotic cardiomyopathy, and apoptotic cardiomyopathies can be rescued by coexpression of a Nix dominant inhibitor lacking the mitochondrial targeting domain (77, 86). We consider that Nix and other factors that may be similarly induced during cardiomyocyte hypertrophic growth sensitize the myocyte to apoptosis, especially when normal protective factors are diminished.

**Autophagy in Heart Failure: What’s on the Menu?**

Like apoptosis, autophagy (Greek *autos*, meaning, self and *phagein*, meaning to eat) is an essential normal cellular process that, in heart failure, goes awry (8). Within the normal homeostatic processes of cell protein replacement, autophagy is the primary mechanism for degradation of large organelles and long-lived proteins through the lysosomal pathway, whereas nonlysosomal degradation of shorter lived and/or regulatory proteins occurs largely via the ubiquitin-proteasome system (9, 15, 25, 47, 48, 60). The histological hallmark of autophagy is the double membrane delimiting autophagosome, which contains proteins destined for degradation and achieves this by fusing with lysosomes (60). Since cardiac hypertrophy is accomplished through massive alterations in normal cardiomyocyte protein homeostasis, with accelerated protein breakdown and synthesis (13), normal proteolytic processes are accelerated. The rate of myocardial protein synthesis is measurably higher than baseline within 6 h of induction of pressure overload and continues to be increased throughout the period of ongoing hypertrophic growth (39). Although protein turnover (synthesis and breakdown) is increased during hypertrophy, it has been suggested that autophagy is actually diminished in response to aortic stenosis and isoproterenol infusion in animal models, possibly reflecting an antinflammatory effect during active hypertrophy (17, 69).

Initially described as a cell survival mechanism in starvation (9, 46), autophagy has recently received a great deal of attention as a mechanism of cell death in other several clinical disorders, including heart failure. Schaper et al. (72) observed autophagosome-like cytoplasmic inclusions in cardiomyocytes from patients with heart failure. These cells also exhibited sarcomeric degeneration, suggesting the possibility that the inclusions represented “autophagic” sarcomeric protein. Frequent autophagic vacuoles staining positively for ubiquitin have also been observed in the myocardium of patients with severe aortic stenosis (33). Remarkably, ubiquitin positivity increased 12-fold in the myocardium of severe aortic stenosis patients with severe left ventricular systolic dysfunction (left ventricular ejection fraction of <30%) compared with patients with preserved ventricular function. Autophagic cell death is also prevalent in human and hamster

**FIGURE 3. Therapeutic strategies to prevent decompensated heart failure**

Hemodynamic stress and myocardial injury provoke development of compensated hypertrophy via neurohormonal signaling, which can be inhibited by neurohormonal antagonists. Cardiomyocyte death provokes transition to decompensated hypertrophy, which is a therapeutic target for antiapoptosis therapies. Attempts to provoke physiological hypertrophy antagonize cardiomyocyte death. Genetic and pharmacological strategies targeted at stimulating antihypertrophic pathways in a novel therapeutic approach to reverse compensated hypertrophy before its irreversible progression to decompensated heart failure.
cardiomyopathies (59, 73) and a model of diphtheria toxin-induced heart failure (3). Finally, mutations in, and deletion of, the gene encoding for lamp2, a critical lysosomal membrane protein, are associated with accumulations of autophagic vacuoles in liver, muscle, and heart cells that mimic the human cardiomyopathic phenotype in Danon disease (15, 78, 84). Together, these observations suggest that autophagy in cardiomyocytes is an essential component of the normal process for renewal of cellular proteins but that conditions of greatly accelerated protein turnover, as in hypertrophied cardiac myocytes that are subjected to additional hemodynamic or metabolic stress, can perturb this normal function and result in cell death (48).

Regression of Pathological Hypertrophy: Through the Looking Glass, Alice

In designing therapeutics that might prevent the progression from compensated hypertrophy to decompensated heart failure, it would be attractive to target one or more of the mechanisms of cell death, i.e., necrosis, apoptosis, and autophagy (FIGURE 3). This is likely to be difficult, however, since the pathways for each are distinct, and apoptosis and autophagy have important physiological roles in nonmyocytes, if not in myocytes themselves. Thus it may be more effective to target hypertrophy itself rather than its progression. One approach would be to modify hypertrophy so that the benefits of increased myocardial mass are not diminished by the unique functional and molecular characteristics of reactive or “pathological” hypertrophy. For example, if hypertrophied myocardium had the characteristics of the athlete’s heart (“physiological hypertrophy”), then progression to heart failure would not be expected to occur. Indeed, endurance training by swimming was demonstrated by Scheuer (67) to be beneficial in rodent heart failure over 30 years ago. Conversely, even intermittent pressure overload (mimicking the intermittent hemodynamic stress of exercise/endurance training) results in development of hypertrophy with the typical pathological features (68). Molecular approaches designed to recapitulate physiological hypertrophy via growth factor pathways or their downstream mediators have shown some promise in experimental models of cardiac disease (44).

Another approach, previously thought to be problematic, is to eliminate reactive hypertrophy altogether. Although the Laplace relationship demonstrates how myocardial hypertrophy can normalize ventricular wall stress, recent data have strongly suggested that hypertrophy of the type that develops in response to hemodynamic overload (“pathological hypertrophy”), may not be either necessary or desirable for functional compensation. Multiple gene or pharmacological manipulations that interfere with critical hypertrophy signaling pathways have suggested that cardiac function is retained after pressure overloading when the hypertrophic response is inhibited (24, 34, 35, 71). Murine models with inhibition of Goq signaling or ablation of the catecholaminergic dopamine β-hydroxylase gene exhibit attenuated hypertrophy but are protected from adverse remodeling and functional deterioration under conditions of pressure overload where ventricular wall stress is elevated (24). This contrasts with the situation in normal mice studied under the same experimental conditions, in which development of reactive hypertrophy tends to normalize wall stress but was nevertheless associated with cardiac enlargement and contractile dysfunction.

If myocardial hypertrophy is not essential for acute functional compensation, then efforts directed at preventing hypertrophy are attractive. Clinically, neurohormonal inhibition with adrenergic, angiotensin, or endothelin antagonists can partially reverse cardiac hypertrophy via multiple mechanisms, including altered loading conditions (66).

With increased understanding of hypertrophy signaling pathways (27), refined approaches are being developed to inhibit pathological hypertrophy, while preserving the beneficial aspects of these signaling pathways (31, 61). For example, whether signaling through a particular pathway is deleterious may depend on the time or duration of activation, such as in the PI3K/Akt pathway, wherein temporally limited signaling is essential for physiological growth (21), but chronic activation can lead to cardiomyopathy (63). Likewise, activation of specific arms of individual signaling cascades may be preferable, such as the MAP-kinase pathways wherein MEK1-ERK signaling seems to promote compensatory hypertrophy (11), but activation of p38 and JNK kinases leads to decompensated cardiomyopathy (51, 88). Indeed, prevention of hypertrophy by inhibition of certain targets such as FAK-focal adhesion kinase, which transduces integrin signaling sensing biomechanical stress and leads to hypertrophy, may be deleterious (18). The increasingly detailed knowledge of interactive hypertrophy signaling pathways provides a conceptual framework that suggests multiple possible strategies to inhibit hypertrophy but also suggests the potential for promiscuous effects of individual therapies based on inter-pathway crosstalk.

A novel approach targeting reactive hypertrophy that is receiving increasing attention is activation of those intrinsic pathways that negatively regulate hypertrophic growth, i.e., endogenous inhibitors of hypertrophy. Some of these anti-hypertrophic signaling pathways are constitutively active in normal myocardium, such as glycogen synthase kinase GSK3β (4), class II histone deactyleases (HDACII) (87), phospholipase A2 (30), thioredoxin (85), and caveolin 3 (42). During periods of hemodynamic stress, the activity of these pathways is suppressed, thus disinhibiting hypertrophic signaling. Other anti-hypertrophic pathways are normally silent but are strongly induced by hemodynamic...
overload, such as cAMP early repressor (ICER), MCIP-1, ANP/BNP, SOCS-3, and tend to restrain the hypertrophic response in a classical negative feedback loop (31). One such inducible anti-hypertrophic factor, which targets the hypertrophic effects of protein kinase C (19), is PICOT (PKC interacting cousin of thioreredoxin) (40). PICOT is induced in pressure overload hypertrophy, and its forced expression in the myocardium reduced pressure overload hypertrophy by ~50%, while significantly enhancing myocardial systolic performance. Another potentially attractive target for inhibiting hypertrophy is histone acetylation/deacetylation by histone acetyl transferase (HAT) and histone deacetylase (HDAC) enzyme system (7). These enzymes modulating the effects of multiple transcription factors and are key regulators of stress-induced pathological myocardial growth, and inhibition of HDACs with broad-spectrum inhibitors has prevented development of pressure overload hypertrophy (43).

**Summary**

A great deal of progress has been made in elucidating the mechanisms of reactive cardiac hypertrophy, and multiple pathways leading to adverse structural and functional remodeling have been delineated. Cardiomyocyte hypertrophy is the nearly universal response to functional cardiac insufficiency, but it may not be essential to physiological adaptation, and it clearly sets the stage for cardiomyocyte death from oncosis, apoptosis, or autophagy. Loss of cardiomyocytes and contractile dysfunction of those that survive are the underlying mechanisms for cardiomyopathy development and progression of heart failure. Strategies directed at modulating myocardial hypertrophy, reversing cardiac remodeling, and preventing cardiomyocyte death through targeting of relevant hypertrophy/death signaling pathways or activation of endogenous anti-hypertrophic mechanisms are promising avenues to addressing the problem of heart failure.

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**References**


60. Sano M, Schneider MD. Still stressed out but doing fine: normalization of wall stress is superflu- ous to maintaining cardiac function in chronic pressure overload. Circulation 105: 8–10, 2002.


