Mechanisms of Disease

Cardiac Plasticity

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The heart is capable of remodeling in response to environmental demands, and a variety of stimuli can induce it to grow or shrink (Fig. 1). Exercise, pregnancy, and postnatal growth promote physiologic growth of the heart, whereas neurohumoral activation, hypertension, and myocardial injury can cause pathologic hypertrophic growth. In contrast to physiologic growth, hypertrophic growth can increase the risk of heart failure and malignant arrhythmia. Atrophy of the heart is a complication of protracted bed rest, prolonged weightlessness during space travel, and mechanical unloading with a ventricular assist device.

In this review, we discuss the three major forms of cardiac plasticity: physiologic growth in response to normal demand, pathologic hypertrophic remodeling in the setting of hemodynamic stress, and cardiac atrophy as an adaptation to ventricular unloading. We outline the principal molecular mechanisms of these growth and antigrowth reactions and discuss how these pathways could be manipulated for therapeutic benefit.

Dynamics of Myocardial Growth

Hypertrophic growth is the primary mechanism by which the heart reduces stress on the ventricular wall. It entails an increase in protein synthesis and in the size and organization of force-generating units (sarcomeres) within individual myocytes. The response of the heart to physiologic demand can be remarkable: left ventricular mass in highly trained athletes exceeds left ventricular mass in nonathletic control subjects by up to 60%. Hypertrophic growth occurs to a similar extent in many forms of heart disease. After surgical constriction of the aorta, cardiac mass can increase substantially within just a few days. By contrast, cardiac mass decreases by as much as 25% after only 1 week of hemodynamic unloading. It is apparent from the increases in left ventricular mass that occur as a result of exercise or pathologic stress that the myocardium has a dynamic growth range of at least 100% (Fig. 2).

Changing Ideas about Cardiac Hypertrophy

Before the Industrial Revolution, physical activity was an integral part of daily life, and athletic endeavors were encouraged; Herodicus, Hippocrates, and Galen all described the benefits of exercise. With the emergence of labor-saving devices in the 19th century, concerns arose about insufficient exercise and the dangers of over-exertion. New terms for overexertion were coined, including “athlete’s heart,” “soldier’s heart,” and “effort syndrome”; all implied danger due to excessive exertion. In the late 19th century, the Swedish physician Henschen was the first to recognize exercise-induced cardiac enlargement. Relying solely on percussion of the chest in cross-country skiers, he detected dilatation and hypertrophy on both sides of the heart and concluded that there was pathologic enlargement of the heart after exercise.
In 1898, an article in the British Medical Journal said, “There must be very few [physicians] who have not seen the ill effects of overexertion on a bicycle.”

In The Principles and Practice of Medicine, William Osler pointed to hypertrophy as a step in the development of heart failure, since it is followed by a “period of broken compensation . . . that commonly takes place slowly and results from degeneration and weakening of the heart muscle.”

Approximately 70 years later, a different view of cardiac hypertrophy began to emerge. In accordance with Laplace’s law, which dictates that afterload-induced increases in systolic wall stress and oxygen consumption are offset by increases in wall thickness, hypertrophic growth of the heart was seen as “compensatory” and hence beneficial. Animal models of pressure overload led Meerson to argue in the 1960s that cardiac growth induced by biomechanical stress plays a protective role, at least in the short term.

Moreover, in the 1970s and 1980s, hemodynamic measurements in patients with valvular heart disease provided support for the concept of adaptive hypertrophic growth, which when “inadequate” could lead to systolic dysfunction. During that time, however, data from the Framingham Heart Study established that left ventricular hypertrophy is a marker for an increased risk of adverse cardiovas-
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The hypertrophic phenotype

Hypertrophy of an organ is due to an increase in the size of its cells. In myocardial growth caused by exercise or pregnancy, cardiac structure and function are normal and there is no association with heart failure.\textsuperscript{23,24} By contrast, abnormal metabolic, structural, and functional events underlie the hypertrophy that occurs in hypertension, obesity, and valvular heart disease; after infarction; or with mutations in genes coding for contractile proteins. In these conditions, the abnormalities include a shift toward glycolytic metabolism, disorganization of the sarcomere, alterations in calcium handling, changes in contractility, loss of myocytes with fibrotic replacement, systolic or diastolic dysfunction, and “electrical remodeling” (i.e., alterations in the expression or function of ion-transporting proteins, or both). Despite the differences between physiologic and pathologic hypertrophy, it is likely that they are not binary, distinct phenotypes, but rather that they represent a continuum of states of cardiac plasticity.\textsuperscript{25}

The classic view is that growth of the heart has three morphologic patterns.\textsuperscript{26} Concentric remodeling is an increase in relative wall thickness but with normal cardiac mass. Concentric hypertrophy is an increase in relative wall thickness and cardiac mass with little or no change in chamber volume. The characteristic of this pattern of growth, which is often the result of pressure overload, is the addition of sarcomeres in parallel and lateral growth of individual cardiomyocytes. Eccentric hypertrophy is an increase in cardiac mass with increased chamber volume. Relative wall thickness may be normal, decreased, or increased. This growth pattern is common under conditions of isotonic exercise or volume overload or after infarction and is distinguished by the addition of sarcomeres in series and longitudinal cell growth.\textsuperscript{24}

No discrete thresholds define the boundaries of excessive cardiac mass (hypertrophy) or inadequate cardiac mass (atrophy). Estimates of cardiac mass depend on measurement techniques. In many studies, left ventricular mass is measured by means of M-mode echocardiography, in which...
mass is calculated with a formula that takes into consideration the left ventricular diameter at end-diastole and the thickness of the left ventricular walls. Estimates of ventricular mass derived from magnetic resonance imaging may be lower — and more precise and accurate — than those derived from echocardiography.

**CONTRASTING PHENOTYPES OF CARDIAC GROWTH**

Among all athletes, rowers, cyclists, and cross-country skiers tend to have the largest hearts, although most of them have a left ventricular wall thickness of less than 1.3 cm (upper limit of normal, 1.1 cm in adults who are not highly conditioned). Athletes who train seasonally have seasonal variation in left ventricular dimensions. Pregnancy-induced heart growth regresses over a period of months after delivery. In Burmese pythons, consumption of a large meal is associated with an increase in metabolic work by a factor of seven and a spectacular 40% increase in ventricular mass within 48 hours after consumption, both of which return to normal within 28 days.

In contrast to these physiologic changes in the heart, pathologic hypertrophy occurs in response to neurohumoral activation, chronically increased hemodynamic load, or other stress on the heart. As with exercise-induced heart growth, pathologic cardiac remodeling can be dramatic and rapid; myosin heavy-chain synthesis increases by as much as 35% within hours after exposure to an elevated afterload. Enforced expression of an activated transgenic Akt1 gene triggers an increase in cardiac mass by 60% in just 2 weeks.

In cardiac hypertrophy, the size of the cardiomyocyte increases, and there is heightened organization of the sarcomere (indicated by bold, parallel bands of sarcomeric proteins on microscopic examination). Exercise-induced hypertrophy is typically not accompanied by an accumulation of myocardial collagen. Expression of thyroid hormone receptors and α-myosin heavy-chain and β-myosin heavy-chain isoforms are regulated in opposite directions in hypertrophy induced by exercise as compared with that induced by pressure overload. Also, physiologic and pathologic hypertrophy differ in their content of myosin isoforms, which may contribute to diminished contractile performance in pathologic hypertrophy. Transcriptional profiling of hearts from exercised rats showed down-regulation of hypertrophic markers (genes with expression that is indicative of the hypertrophic phenotype). Pressure and volume stress trigger distinct patterns of expression of β-myosin, α-skeletal actin, and sarcoplasmic reticulum Ca²⁺-ATPase, despite similar degrees of hypertrophy and induction of atrial natriuretic factor. Recent evidence suggests that it is the nature of the stimulus, not whether it is intermittent or sustained, that determines the phenotype in hypertrophic remodeling.

Because the growth of the heart eventually plateaus even in the face of persistent stress and subsides when growth signals abate, pathways that antagonize cellular enlargement must play a role in regulating heart size. Simple deactivation of hypertrophic pathways is unlikely. In skeletal and heart muscle, activation of pro-growth signaling cascades is accompanied by inhibition of pathways that promote proteolysis; the converse pertains under conditions leading to atrophy. Cardiomyocyte plasticity is often accompanied by reinduction of the “fetal gene program,” in which patterns of gene expression mimic those seen during embryonic development.

**FUNCTIONAL DECOMPENSATION IN PATHOLOGIC CARDIAC HYPERTROPHY**

With prolonged stress, the heart undergoes apparently irreversible decompensation, resulting in dilatation of the failing heart. Inherited forms of heart disease can progress similarly, from hypertrophic cardiomyopathy to dilatation or directly to dilated cardiomyopathy. Late-phase remodeling events leading to heart failure are associated with perturbations of cellular Ca²⁺ homeostasis and ion currents. Prominent among the morphologic changes associated with these events are increased apoptosis, fibrosis, and chamber dilatation. These changes occur in aortic stenosis and in certain forms of familial hypertrophic cardiomyopathy. In animal models, the stress–response pathways that induce ventricular growth can also cause systolic dysfunction, ventricular dilatation, and a syndrome compatible with clinical heart failure. However, the mechanisms that determine how
long-standing hypertrophy ultimately progresses to heart failure are poorly understood.

Decompensation is associated with thinning of the ventricular walls by a combination of proteolysis and death of myocytes. An early hypothesis held that blood supply that is insufficient to meet the demands of the thickened myocardium results in ischemia; some studies provide support for this idea and others do not.\textsuperscript{35,52,53} Other potential mechanisms include alteration of contractile proteins,\textsuperscript{38} remodeling of the extracellular matrix with consequent fibrosis,\textsuperscript{54} and changes in activation of the β-adrenergic pathway.\textsuperscript{55,56} Recent studies have implicated autophagy, a process of protein and organelle recycling,\textsuperscript{57,58} in the response of the cardiomyocyte to stress and the transition to cardiac failure.\textsuperscript{59-63}

**MYOCARDIAL ATROPHY**

Decreases in cardiac mass to levels that are well below normal occur in conditions of weightlessness, bed rest, and other states of ventricular unloading. In a study involving healthy subjects assigned to 12 weeks of bed rest, the left-ventricular-mass index decreased by 15%.\textsuperscript{64} In a study that probably defined the lower limit of the size of the atrophied heart, de Groot et al. reported a 25% decrease in left ventricular mass in patients with spinal cord injury who did not exercise.\textsuperscript{65}

As with other forms of cardiac remodeling, ventricular atrophy occurs rapidly. In a canine model of ventricular unloading induced by constriction of the inferior vena cava, a 26% decrease in left ventricular mass occurred within 10 days.\textsuperscript{66} After the return of afterload to normal by replacement of a stenotic aortic valve in humans, there is regression of myocyte hypertrophy and reduction in left ventricular mass and interstitial fibrosis within several weeks, although reversion of each remains incomplete for as long as 6 years after surgery.\textsuperscript{67,68} In mice, deactivation of overexpressed Akt1 leads to a 40% decrease in cardiac mass in just 1 week.\textsuperscript{35}

Muscle atrophy is an energy-requiring process with mechanisms that are just now being deciphered. In all types of atrophying muscle, the ubiquitin–proteasome system is activated, and it catalyzes the degradation of the bulk of muscle proteins, especially myofibrillar components.\textsuperscript{69} In skeletal muscle, atrophy requires activation of ubiquitin ligases (also called “atrogenes”).\textsuperscript{44,70-72} In cardiac muscle, negative regulators of growth act through suppression of pro-growth pathways or direct stimulation of protein degradation.\textsuperscript{46,73-79} Beyond that, we know little about mechanisms governing cardiac atrophy.

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**SIGNAL TRANSDUCTION IN CARDIAC GROWTH**

Two of the major triggers of cardiac hypertrophy—biomechanical stress and neurohumoral factors—induce intracellular signaling cascades that promote protein synthesis, protein stability, or both, with consequent increases in cardiomyocyte size (Fig. 3). The mechanisms whereby biomechanical signals are transduced across the cell membrane are unclear, but they probably involve stretch-sensitive ion channels, integrins, and other structural proteins in a complex network that links the extracellular matrix, the cytoskeleton, the sarcomere, Ca\textsuperscript{2+}-handling proteins, and the nucleus.\textsuperscript{80} The primary effect of inherited mutations in proteins of the sarcomere or cytoskeleton that cause familial hypertrophic cardiomyopathy or dilated cardiomyopathy is probably an alteration of contractile efficiency, but how these mutations influence biomechanical transduction is not known.\textsuperscript{80}

Mechanical stress elicits paracrine and autocrine signaling by inducing synthesis and secretion of potent growth factors, which include insulin-like growth factor I, angiotensin II, and endothelin-1, in both cultured cells\textsuperscript{80} and in patients with aortic stenosis.\textsuperscript{81} Mechanical stretch is capable of activating angiotensin II receptors in cardiomyocytes directly, without involvement of angiotensin II.\textsuperscript{82}

Whereas numerous signaling pathways have been implicated in stress-induced remodeling of the heart,\textsuperscript{83} there is general agreement that altered intracellular calcium homeostasis is a proximal trigger of the process.\textsuperscript{83} Several calcium-dependent signaling molecules, including calcium-dependent protein kinases and mitogen-activated protein kinases, participate in the transduction of hypertrophic stimuli.\textsuperscript{84-86} Upstream of this pathway, signaling can occur through the G\textsubscript{q} heterotrimeric G protein. In cardiac growth triggered by physiologic demand, signaling through peptide growth factors and consequent activation of the phosphatidylinositol 3’-kinase (PI3K)–Akt signaling pathway is a major mechanism,\textsuperscript{87} although long-term activation of Akt triggers pathologic hypertrophy, impaired coronary angiogenesis, and cardiomyopathy.\textsuperscript{35}
The calcium–calmodulin–dependent phosphatase calcineurin is an especially potent inducer of hypertrophy. It is sufficient, and in many cases necessary, for pathologic cardiac growth. Calcineurin activity in the mouse heart increases in response to pressure overload or myocardial infarction, and calcineurin is activated in the cardiac hypertrophy that is induced by aortic stenosis and in heart failure. Unlike calcineurin signaling in cardiac muscle, calcineurin signaling in skeletal muscle — and consequent induction of slow-twitch, oxidative fibers — appears to be beneficial. Taken together, signaling events governing cardiac plasticity constitute a network that integrates a multitude of signals to activate a limited number of responses (Fig. 4).

**CARDIAC PLASTICITY IN HEART DISEASE**

Hypertension is the most important risk factor for heart failure; this is consistent with a major role of hypertrophic myocardial growth in the development of heart failure. The prevailing view of hypertensive heart disease is that it leads first to concentric left ventricular hypertrophy, then to ventricular dilatation and impaired contractility. There is a relation between the amount of increase in cardiac mass and the occurrence of adverse clinical events. However, in addition to simple measures of left ventricular mass, the pattern of hypertrophic remodeling is relevant: subtle systolic dysfunction can occur with concentric remodeling in hypertension, whereas with eccentric hypertrophy there is more severe dysfunction. Eccentric hypertrophy has also been found to be associated with worse systolic function in a subgroup of patients with hypertension; these findings are consistent with epidemiologic data linking left ventricular dilatation with the development of heart failure. For these reasons, the extent to which left ventricular hypertrophy is a risk factor for systolic dysfunction may depend on whether the hypertrophy is concentric or eccentric.

Cardiac atrophy can also have important clinical implications. In hearts that have been subjected to therapy with a ventricular assist device, and hence have become atrophic, clinically significant recovery of function sometimes occurs, although the mechanism is obscure. There are several causes of orthostatic hypotension immediately after a person returns to earth after space travel, including volume depletion and poorly understood decreases in peripheral vascular resistance. However, given that the left-ventricular-mass index decreases by an astounding 1% per day in space, cardiac atrophy is thought to play an important role.

**PROSPECTS FOR THERAPY**

A major objective of treatment of heart failure is to blunt mechanisms that contribute to pathologic...
cardiac remodeling while preserving contractile function and myocyte viability. Mainstays of therapy include afterload reduction, blockade of the beta-adrenergic and renin–angiotensin–aldosterone axes, and use of mechanical support devices in patients with advanced disease. These strategies, which aim to delay or even reverse maladaptive remodeling, are supported by considerable clinical evidence.

Preclinical studies have shown that blunting hypertrophic growth is possible without compromising the contractile performance of the heart. These studies have uncovered a potential new target of antiremodeling therapy: the hypertrophic phenotype itself. This strategy is based on the notion, which is still debated, that suppressing pathologic hypertrophy may be key to impeding progression to heart failure. Some clinical evidence provides support for therapeutic targeting of the hypertrophic process.

Other experimental treatments target nitroso-oxidative stress or alterations in myocyte energetics. Activation of physiologic growth by means of exercise, activation of PI3K–Akt signaling, or treatment with growth hormone may be beneficial in patients with heart failure. Very recent studies point to microRNAs (small, noncoding RNAs that form base pairs with specific messenger RNAs [mRNAs] and inhibit translation or promote mRNA degradation) as both sufficient and necessary for stress-dependent cardiac growth.

As we move to translate these advances to the bedside, the difficulties that are inherent in drug trials for heart failure will be considerable. An incremental benefit above and beyond that provided by current therapy must be demonstrated, and new strategies should be cost-effective. With respect to hypertrophy, therapy requires reversal, not simply prevention. Clinical end points are complex; hypertrophy may not be a reliable end point, and monitoring fetal gene activation in myocytes is obviously problematic. Finally, studies
with mortality end points are inherently expensive and time-consuming, and they require large numbers of patients.

LIMITATIONS AND PERSPECTIVE

A detailed dissection of mechanisms governing cardiac plasticity raises the prospect of enhancing the advantageous features of hypertrophy (e.g., decreased wall stress) while inhibiting the maladaptive features (e.g., decompensation, arrhythmogenesis, and contractile isoform switching). However, many recent molecular advances have relied heavily on studies of sedentary, caged rodents, especially genetically engineered mice. Surely there are important differences between these animal models and humans. The human heart rate is 10 times slower than that of mice, and the human ventricular ejection fraction is substantially lower. In addition, Ca\(^{2+}\) handling in mice relies to a greater extent on transsarcolemmal transport than on transsarcolemmal transport. Studies showing that inhibition of cardiac hypertrophy is beneficial despite persistence of the initiating stimulus have been short term (approximately 10 to 15% of a normal mouse life span); 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 atrophy. Finally, acute increases in pressure stress induced by aortic banding may not faithfully mimic the conditions of chronic, low-level hemodynamic load such as that which occurs in hypertension.

Enormous effort has been directed toward identifying new therapeutic strategies with long-term efficacy in heart failure. The path is littered with failures,\(^{123}\) yet advances in myocardial biology, stem-cell research,\(^{124}\) and mechanical devices\(^ {125,126}\) hold promise for future treatments. Urgency is highlighted by the fact that heart failure is already the most important cardiovascular disorder in the Western world from the perspective of use of resources.\(^ {127}\) A comprehensive view of myocardial plasticity will be obligatory, since it is likely that strategies for suppressing excessive activation of pathologic signaling pathways must be precisely regulated to avoid disrupting homeostatic mechanisms. Major challenges remain, but patients with heart disease are likely to benefit from these efforts.

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