Molecular Pathways Underlying Cardiac Remodeling During Pathophysiologic Stimulation

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Cardiac remodeling involves molecular, cellular, and interstitial changes that manifest clinically as changes in size, shape, and function of the heart after injury or stress stimulation. Although the term cardiac remodeling was initially coined to describe the prominent changes that occur after myocardial infarction, it is clear that similar processes transpire after other types of injury such as with pressure overload (aortic valve stenosis, hypertension), inflammatory disease (myocarditis), idiopathic dilated cardiomyopathy, and volume overload (valvular regurgitation). Although the causes of these diseases are different, they share molecular, biochemical, and cellular events to collectively change the shape of the myocardium.

Cardiac hypertrophy is a common type of cardiac remodeling that occurs when the heart experiences elevated workload. The heart and individual myocytes enlarge as a means of reducing ventricular wall and septal stress when faced with increased workload or injury. Cardiac hypertrophy is classified as “physiological” when it occurs in healthy individuals after exercise or pregnancy and is not associated with cardiac damage. In contrast, hypertrophy that results from pressure or volume overload or after myocardial infarction is usually referred to as “pathological.” This name may be misleading, however, because pathological hypertrophy may also involve a compensatory and adaptive phase that tends to reduce wall stress and maintain output, although ultimately these positive aspects are lost and ventricular function declines, often leading to heart failure.

Pathological Remodeling
In addition to ventricular remodeling, pathological cardiac hypertrophy involves cellular and molecular remodeling such as myocyte growth without significant proliferation, reexpression of fetal genes, alterations in the expression of proteins involved in excitation-contraction coupling, and changes in the energetic and metabolic state of the myocyte. These cellular and molecular changes within the myocyte are accompanied by changes in the extracellular matrix (ECM) and by myocyte death caused by necrosis or apoptosis. As the heart transitions from compensated hypertrophy to dilated heart failure, these cellular and molecular changes intensify, resulting in myocyte lengthening, ECM remodeling, chamber dilation, and impaired systolic and/or diastolic function.

Macrosopically, the heart responds to injury and stress in various ways. Immediately after a myocardial infarction, the injury area expands, followed by regional dilation and thinning of the infarct zone. As the heart subsequently scarifies and remodels, its geometry changes such that it becomes less elliptical and more spherical with thinner walls. Similarly, in volume overload hypertrophy, the internal radius of the ventricle increases, resulting in eccentric hypertrophy. In contrast, pressure overload stress usually produces increased left ventricular (LV) wall thickness without or with little increase in chamber size, in a process called concentric hypertrophy (Figure 1A).

Whole organ remodeling and hypertrophy are usually associated with similar changes at the cardiomyocyte cell level (Figure 1B). Eccentric hypertrophy is characterized by assembly of contractile-protein units in series, leading to a relatively greater increase in the length than in the width of myocytes. This type of growth can be even more pronounced in forms of cardiac dilation in which the heart increases in size, but only through lengthening of myocytes with addition of sarcomeres in series, usually with a loss of cell width. In contrast, pressure overload–induced concentric hypertrophy is characterized by assembly of contractile-protein units in parallel, resulting in a relative increase in the width of individual cardiac myocytes. Nevertheless, macroscopic events do not always follow myocyte cell hypertrophy. For example, after myocardial infarction, cardiomyocyte length and width are increased, whereas regional ventricular wall thickness can be decreased. The apparent discrepancy can be explained by the reduction in myocyte number, slipping between myocytes and the ECM, and changes in wall architecture.

Concentric hypertrophy may progress to eccentric hypertrophy and then to frank dilation with associated systolic heart failure, as observed in animal models with long-term pressure overload stress due to aortic banding (Figure 2). However, the adaptive and maladaptive aspects of concentric hypertrophy are still highly controversial. For example, a study following patients with increased LV mass and normal LV systolic function for 5 years showed that only 12.3% of...
patients in the highest quartile of LV mass developed any detectable LV dysfunction, and only 6.9% of these patients developed clinical heart failure. These observations underscore the need to differentiate the pathways responsible for the initial compensated hypertrophic growth phase from those promoting decompensation, dilation, and extreme ventricular remodeling.

### Physiological Hypertrophy and Associated Signaling Pathways

In humans, isostonic exercise (swimming and running) has been associated with an increase in chamber dimensions and a proportional increase or absence of change in wall thickness. It has long been appreciated that hypertrophy imposed by hypertension or other disease-causing stimuli is distinctly different from the type of hypertrophy and ensuing effects associated with physical training. For example, physiological hypertrophy does not induce fibrosis or reactivation of the fetal gene program, nor is it a risk factor for arrhythmia, reductions in cardiac function, or future heart failure. An interesting question about the stimuli inducing physiological and pathological hypertrophy is whether it is the nature of the stress or the chronicity of the stress. For example, it is possible that the intermittent nature of exercise underlies its benefit, but if exercise stress were applied chronically, it would lead to pathology. To address this question, Rockman and colleagues performed a modified surgical technique in which pressure overload stimulation was applied intermittently with a reversible ligation around the aorta to mimic brief periods of an “exercise-like response.” Intermittent pressure overload resulted in histological and cellular abnormalities with diastolic dysfunction and vascular rarefaction, suggesting that it was the nature of the stimulus and not its duration that was pathological.

Cardiac physiological hypertrophy is largely mediated by signaling through insulin-like growth factor-1 and growth hormone and is transduced by phosphoinositide 3-kinase (PI3K)/Akt signaling. Growth factors such as insulin-like growth factor-1 and insulin bind to their membrane-bound tyrosine kinase receptors and activate a 110-kDa lipid kinase PI3K group I. PI3K phosphorylates the membrane phospholipid phosphatidylinositol 4,5 bisphosphate and recruits the protein kinase Akt (also known as protein kinase B) and its activator, 3-phosphoinositide–dependent protein kinase-1, to the cell membrane. This colocalization leads to phosphorylation and activation of Akt.

The central role of the insulin-like growth factor-1/PI3K/Akt pathway in exercise-induced hypertrophy was suggested in mice expressing constitutively active or dominant-negative mutants of PI3K specifically in the heart. Cardiac-specific expression of constitutively active PI3K resulted in mice with larger hearts, whereas dominant-negative PI3K resulted in mice with smaller hearts. The increase or decrease in heart size was associated with a comparable increase or decrease in myocyte size and, importantly, was not associated with interstitial fibrosis or contractile dysfunction. As expected, hypertrophy in PI3K mice was also not associated with reactivation of the fetal gene program. With respect to loss of function, cardiac expression of dominant-negative PI3K attenuated exercise-induced hypertrophy due to swimming training but not the hypertrophy induced by pressure overload, demonstrating the specificity and importance of this pathway for adaptive hypertrophy. Consistent with these results, cardiac-specific deletion of the insulin-like growth factor-1 receptor blocked exercise-induced cardiac hypertrophy.

Of the 3 Akt genes, only Akt1 and Akt2 are highly expressed in the heart. Cardiac-specific overexpression of constitutively active Akt mutants induced myocyte growth, although at high levels of sustained Akt expression the induced growth was pathological. However, expression of Akt conferred protection from ischemia-induced cell death and cardiac dysfunction, whereas overexpression of a nuclear-targeted isoform of Akt was also cardioprotective at all times and never led to dysfunction. Akt1 gene–deleted
mice weigh ≈20% less than wild-type animals and have a proportional reduction in size of all somatic tissues, including the heart. More importantly, Akt1−/− mice were resistant to exercise-induced cardiac hypertrophy, although they developed greater cardiac hypertrophy in response to aortic constriction. Thus, although the actions of Akt are complex, the evidence suggests that it has a role in the normal growth of the heart and adaptive physiological hypertrophy.

**Concentric Hypertrophy and a Known Transducing Signaling Pathway**

Several pathways and factors appear to induce hypertrophy that is most consistent with a concentric, pressure overload–like response (Figure 3). One such pathway is the extracellular signal-regulated kinases 1/2 (ERK1/2) signaling branch of the greater mitogen-activated protein kinases (MAPKs). The MAPK cascades are composed of multiple levels of kinases that constitute a phosphorylation-based amplification network. Receiving input from membrane-associated G proteins are the MAP3Ks, which in turn activate the MAP2Ks, which next activate the MAPKs. The MAPK cascades are generally subclassified into 3 main branches, consisting of p38 kinases, c-Jun N-terminal kinases (JNKs), and ERK1/2. However, additional kinases in this cascade include ERK5, which is activated by MEK5, and ERK3/4. Signaling through the ERK1/2 cascade is classically initiated at the cell membrane by activation of the small G protein Ras, which then recruits the MAP3K Raf-1 to the plasma membrane, where it is activated. Other MAP3Ks such as MEKK1 may also be involved in ERK activation under specific conditions.
These MAP3Ks then phosphorylate and activate the dual-specificity kinases MEK1 and MEK2 (MAP2Ks) that serve as dedicated kinases for ERK1/2 phosphorylation on closely linked threonine and tyrosine residues in an activation loop domain. Transgenic mice overexpressing an activated MEK1 mutant under the transcriptional control of the cardiac-specific α-myosin heavy chain promoter showed ERK1/2 activation and a phenotype of profound concentric hypertrophy. At the microscopic level, cardiomyocytes exhibited increased width and surface area, akin to the changes observed with pressure overload stress. Importantly, these mice did not show pathological signs of hypertrophy such as fibrosis or sudden death, suggesting that the MEK1-ERK1/2 pathway may be a beneficial component of the compensated, concentric hypertrophy response.

**Eccentric Hypertrophy and a Known Transducing Signaling Pathway**

Eccentric hypertrophy occurs in response to volume overload states such as mitral or aortic valve regurgitation. As discussed above, eccentric hypertrophy is characterized by a preferential addition of sarcomeric units in series, which can increase the shortening capacity of the myocyte and help to preserve ventricular function. However, eccentric hypertrophy with elongation of myocytes is also a hallmark of the transition from compensated hypertrophy in pressure overload conditions to decompensation and failure. Therefore, similar to our discussion for concentric hypertrophy, it is important to distinguish between the adaptive elongation of the cardiomyocyte and the elongation associated with failure. In contrast to ERK1/2, which induces pressure overload–like concentric hypertrophy, the related MEK5-ERK5 branch of the MAPK cascade appears to preferentially induce eccentric hypertrophy.

MEK5 is a highly specific dual-specificity ERK5 kinase and does not activate other MAPKs, even when overexpressed in cultured cells. MEK5-ERK5 signaling has been shown to be activated by growth stimuli including serum and ligands for tyrosine kinase receptors and G protein–coupled receptors. Mice overexpressing an activated mutant of ERK5 appeared normal at 3 weeks but exhibited pronounced ventricular dilation by 6 weeks of age with extremely thin walls of both the right ventricular and LV chambers relative to wild-type hearts. Microscopically, sections from these hearts showed decreases in the transverse cross-sectional area of myocytes, and tissue culture experiments showed elongation of myocytes. Apart from the abnormal hypertrophy of cardiomyocytes, activated MEK5 transgenic hearts seemed otherwise healthy. Masson’s trichrome staining did not reveal evidence of fibrosis, and terminal deoxynucleotidyl transferase dUTP nick end labeling assays did not suggest elevated cell death in dilated MEK5 hearts compared with wild-type hearts. Once again, analysis of the MEK5 mice suggested that growth changes in cardiomyocytes by selected molecular pathways can lead to whole organ remodeling, such as an eccentric/dilated type of growth.

## Pathological Hypertrophic Pathways (Calcineurin and Ca²⁺/Calmodulin-Dependent Kinase II)

Although some of the aforementioned models mainly affect the growth of the myocyte in an eccentric or concentric manner without other signs of pathology, other signaling pathways appear to be strictly cardiomyopathic, whether it is classified as concentric or eccentric or dilated growth (Figure 3). One such pathway is mediated by the calcium/calmodulin-activated protein phosphatase calcineurin. Calcineurin is activated by sustained elevation in intracellular calcium, which facilitates binding to its primary downstream effector, nuclear factor of activated T cells (NFAT). NFAT transcription factors are normally hyperphosphorylated and sequestered in the cytoplasm but rapidly translocate to the nucleus after calcineurin-mediated dephosphorylation. Activation of the calcineurin-NFAT pathway in the heart, such as in transgenic mice overexpressing an activated mutant of calcineurin, causes a dramatic increase in heart size. Cardiomyocytes from calcineurin transgenic hearts are disorganized and markedly hypertrophic, with cross-sectional areas almost double those of wild-type myocytes. The hearts of calcineurin transgenics contained extensive deposits of collagen and extreme activation of the molecular hypertrophic program. Inhibition of calcineurin-NFAT signaling, such as in calcineurin Aβ⁺/− and Nfatc3−/− and Nfatc2−/− mice, has been shown to abate pathological cardiac hypertrophy after pressure overload stimulation or neuroendocrine agonist infusion.

Another molecule that appears to be central to the pathological hypertrophy response in the heart is Ca²⁺/calmodulin-dependent kinase II (CaMKII). CaMKII expression and activity are increased in failing human myocardium and in many animal models of cardiac hypertrophy and heart failure. For example, CaMKII levels are increased and its phosphorylation is elevated after pressure overload in mice. Transgenic mice that overexpress CaMKII developed significant cardiac dilation with reduced function, cardiomyocyte enlargement, and fibrosis, suggesting that CaMKII is involved in the pathological response to stress. Conversely, mice with deletion of CaMKIIδ showed either no change in one group or reduced hypertrophy after pressure overload stimulation in another group. However, there is better agreement that mice lacking CaMKIIδ showed reduced propensity to heart failure or secondary pathological effects after pressure overload. Taken together, these observations suggest that CaMKII plays a role in the pathological hypertrophy response.

## Antihypertrophic Signaling Pathways

Several pathways appear to be antihypertrophic or protective, working to counterbalance stress-induced remodeling and pathological changes in the myocardium. Atrial natriuretic peptide (ANP) and B-type natriuretic peptide are reexpressed in the adult heart in response to injury or neuroendocrine stress stimulation (Figure 3). The natriuretic peptides are hormones that affect blood pressure and plasma volume status through potent natriuretic, diuretic, and vasodilator activities. However, they also signal locally in the cardiac...
myocyte, where they can antagonize hypertrophy. Transgenic mice overexpressing ANP have lower heart weight and blood pressure than wild-type mice.\(^3\) Importantly, ANP-null mice fed a low-salt diet exhibit concentric LV hypertrophy despite blood pressures similar to those of wild-type mice.\(^3\) Mice lacking the ANP receptor (guanylyl cyclase-A) specifically within cardiac myocytes also show enhanced cardiac hypertrophy.\(^3\) These observations suggest that ANP plays an important role in protecting against the development of cardiac hypertrophy independently of blood pressure. The signaling cascades responsible for the antihypertrophic actions of ANP on the heart have not been fully elucidated but likely include cGMP-dependent protein kinases (PKG).\(^4\) For example, transgenic mice engineered to overexpress a catalytic fragment of constitutively active guanylate cyclase of the ANP receptor exhibited an increase in intracellular concentration of cGMP and a decreased hypertrophic response to pressure overload or adrenergic stimulation.\(^5\)

Nitric oxide has also been recognized as a negative regulator of the hypertrophic response. The antihypertrophic effects of nitric oxide are mediated via the second messenger cGMP, which then activates PKG. Studies have suggested that this antihypertrophic effect of PKG is regulated through inhibition of the calcineurin-NFAT signaling pathway.\(^6\) cGMP is catalyzed by specific members of the phosphodiesterase superfamily, predominantly by PDE5A. PDE5A was shown to be expressed in the myocardium,\(^7\) and PDE5A inhibition in the setting of pressure overload prevents and reverses cardiac chamber, cellular, and molecular remodeling.\(^8\) Consistent with previous observations, PDE5A inhibition by sildenafil blunted the activation of ERK and calcineurin-NFAT signaling pathway, suggesting that cGMP antihypertrophic activity stemmed from the inhibition of these pathways.\(^9\)

The L-type calcium channel is the predominant calcium influx pathway in cardiomyocytes for initiation of contraction and communication with the ryanodine receptor in the sarcoplasmic reticulum. T-type calcium channels are reexpressed in adult ventricular myocytes during pathological hypertrophy,\(^10\) although their physiological function is not clear. Surprisingly, mice with inducible cardiac-specific transgenic expression of α1G, which generates T-type current, showed no cardiac pathology despite large increases in calcium influx and in fact were partially resistant to pressure overload-, isoproterenol-, and exercise-induced cardiac hypertrophy.\(^11\) Conversely, α1G-null mice displayed enhanced cardiac hypertrophy after pressure overload or isoproterenol infusion. Mechanistically, α1G was shown to interact with nitric oxide synthase-3, which augmented PKG activity in the heart after pressure overload stimulation. Thus, reexpressed α1G during pathological cardiac hypertrophy may bind to nitric oxide synthase-3 to provide a local calcium signal to induce its activation, leading to blunted hypertrophy through local cGMP and PKG.

Another signaling intermediate that can restrain the cardiac growth response to physiological and pathological stimuli is the small GTPase Cdc42. The level of activated (GTP-bound) Cdc42 increases in the heart after pressure overload or in response to multiple agonists. Mice with a heart-specific deletion of Cdc42 developed greater cardiac hypertrophy after pressure overload and transitioned more quickly into heart failure than did wild-type controls,\(^12\) demonstrating the antihypertrophic and protective properties of Cdc42. Mechanistically, Cdc42 signaled directly to MEK1 in cardiomyocytes, which in turn altered MKK4/7 activity, leading to reduced JNK signaling. Indeed, when Cdc42-deleted mice were crossed with transgenic MKK7 mice, they no longer exhibited an enhanced growth response. Thus, Cdc42 signaling appears to be connected to a JNK antihypertrophic signaling mechanism. The antihypertrophic effect of JNK was previously suggested in Jnk1/2 gene-targeted mice and transgenic mice expressing dominant-negative JNK1/2, which each showed enhanced myocardial growth after stress stimulation.\(^13\) JNK can directly phosphorylate NFAT and prevent its nuclear accumulation, suggesting complex cross-talk between Cdc42, JNK, and NFAT signaling in the regulation of hypertrophy. Similarly, p38 MAPK signaling can also have an antihypertrophic effect in the heart through NFAT inhibition.\(^14\)

### Chromatin Alterations in Cardiac Hypertrophic Signaling

Many of the aforementioned kinases and phosphatases communicate their signals to the nucleus, thereby altering cardiac gene expression. The alterations in gene expression may be mediated by direct regulation of transcription factors or by modulation of transcriptional accessory proteins. For example, the regulation of histone acetylation can profoundly alter global gene expression, such as through increased activity of the histone acetyltransferases p300 and CREB-binding protein. CREB-binding protein and p300 are transcriptional coactivators that can cause the relaxation of chromatin structure and promote gene activation. Overexpression of CREB-binding protein/p300 is sufficient to induce hypertrophy and LV remodeling in transgenic mice, resulting in eccentric LV hypertrophy accompanied by acetylation of cardiac nuclear proteins such as GATA-4 and MEF2 transcription factors.\(^15\) Specific reduction of p300 content or activity diminishes stress-induced hypertrophy and slows the development of heart failure.\(^16\) In agreement with these observations, p300 transgenic mice showed significantly more ventricular dilatation and diminished systolic function after myocardial infarction than wild-type mice.\(^17\)

Histone deacetylases (HDACs) also remodel chromatin but instead are thought to generally repress gene expression and commensurately alter the cardiac hypertrophic response.\(^18\) HDACs are a large group of enzymes that can be divided into 3 main classes: class I HDACs (HDACs 1, 2, 3, and 8), class II HDACs (HDACs 4, 5, 6, 7, 9, and 10), and class III HDACs (sirtuins). Mice lacking HDAC 9 or HDAC 5 showed enhanced hypertrophy in response to pathological stimuli, suggesting that class II HDACs are antihypertrophic modifiers.\(^19\) In contrast, class I HDACs are considered to play a prohypertrophic role.\(^20\) The sirtuins are unique in that they require nicotinamide adenine dinucleotide for catalytic activity, and Sirt3 levels are elevated during hypertrophy. Sirt3-deficient mice showed signs of cardiac hypertrophy and interstitial fibrosis at 8 weeks of age. Application of hyper-
trophic stimuli to these mice produced a severe cardiac hypertrophic response, whereas Sirt3-expressing transgenic mice were protected from similar stimuli.57 These results suggest that the class III HDAC Sirt3, similar to the class II HDACs, is an endogenous negative regulator of cardiac hypertrophy.

**Molecular Changes Underlying a Transition to Heart Failure**

The mechanisms responsible for the transition from compensated to decompensated hypertrophy are under intense investigation. Phenotypically, this transition includes intrinsic changes in the cardiomyocyte such as reexpression of fetal genes, alterations in the expression of proteins involved in excitation-contraction coupling, and changes in the energetic and metabolic state of the myocyte. The transition to decompensated hypertrophy also includes a mismatch between vascular and cardiomyocyte growth, myocyte death caused by necrosis and apoptosis, and changes in the extracellular matrix. Here we will highlight recent work in a few of these areas that might hold therapeutic potential.

**Impaired Excitation-Contraction Coupling**

Impaired calcium homeostasis is a prominent feature in the transition from compensatory hypertrophy to heart failure, which manifests as contractile dysfunction and development of arrhythmias.58 Although we will not attempt to review this entire subject, we will highlight a few molecular targets involved in this process. Protein kinase Ca (PKCa) may be one such regulator that alters calcium handling in the heart and leads to greater decomposition and heart failure. In the mouse heart, activation of PKCa suppresses sarco(endo)plasmic reticulum calcium cycling by phosphorylating protein phosphatase inhibitor 1, leading to reduced activity of SERCA2 by rendering phospholamban less phosphorylated.59

Conversely, hearts of Pkca-deficient mice were hypercontractile and showed increases sarco(endo)plasmic reticulum calcium loads and increased phospholamban phosphorylation.59 Pkca-deficient mice were also protected from 3 different models of heart failure, suggesting that this kinase is normally involved in worsening heart disease and promoting decomposition. Similarly, short-term pharmacological inhibition of the conventional PKC isoforms (including PKCa) significantly augmented cardiac contractility in wild-type mice and in different models of heart failure in vivo but not in Pkco-deficient mice.60,61 Collectively, these results suggest that PKCa inhibition could be a novel therapeutic strategy to antagonize the transition to heart failure by addressing a known dysregulation in calcium homeostasis and contractile performance.

S100A1 is a member of the multigenic EF-hand calcium-binding S100 protein family. This calcium sensor colocalizes and interacts with the SERCA2/phospholamban complex and modulates both systolic and diastolic RyR2 function and cardiomyocyte sarco(endo)plasmic reticulum calcium release, respectively.62 Chronically failing human myocardium is characterized by progressively diminished S100A1 mRNA and protein levels that inversely correlate with the severity of the disease.62 That this downregulation might be pathological is consistent with observations in S100A1-null mice that showed enhanced susceptibility to functional deterioration in response to chronic cardiac pressure overload stress and ischemic damage.63,64 In contrast, mice with overexpression of S100A1 are hypercontractile and maintained almost normal LV function after myocardial infarction.64

**Vascular and Cardiomyocyte Growth Mismatch**

Hypertrophy and cardiomyopathy dynamically alter myocardial oxygen demand and perfusion through the coronary circulation. Pathological hypertrophy is correlated with a reduction in capillary density, possibly leading to myocardial hypoxia or microischemic areas that reinforce pathology.65 In a mouse model of severe transverse aortic constriction, the number of microvessels per cardiomyocyte increases until day 14 (compensated phase) and then decreases thereafter until frank rarefaction is observed (decompensation).66 Vascular endothelial growth factor (VEGF) is an endothelial cell mitogen that has an essential role in both vasculogenesis and angiogenesis. In addition to endothelial cells, VEGF is also secreted from cardiomyocytes in response to extracellular stimuli.67 Mice with cardiomyocyte-specific deletion of VEGF-A exhibit reduced capillary density and impaired contractility, suggesting that VEGF secretion from the cardiomyocyte is important for maintenance of cardiac function.68 Repression of VEGF signaling by an adenoviral vector encoding a decoy VEGF receptor in a murine model of pressure overload hypertrophy resulted in reduced myocardial capillary density, accelerated contractile dysfunction, and pathological cardiac remodeling.69 Reciprocally, introduction of angiogenic factors during pressure overload enhances the increase in the number of microvessels, preserving the hypertrophic response in a compensated state.68 Mechanistically, Hif-1α, a key transcription factor for the hypoxic induction of angiogenesis, is increased by pressure overload in the mouse, and conditional deletion of this gene resulted in reduced expression of VEGF, lower number of microvessels, significantly attenuated cardiac hypertrophy, and greater heart failure.68 In the same study, it was shown that p53 accumulation is essential for the transition from cardiac hypertrophy to heart failure through inhibition of Hif-1α. p53 may induce Hif-1α degradation through Mdm2, a ubiquitin E3 ligase target gene, although p53-mediated HIF1α ubiquitination and degradation are reversed by the activation of PKB/Akt and are independent of Mdm2.70

**Changes in the ECM**

Ventricular and cellular remodeling in the heart also involves changes in the ECM and associated collagen network that surrounds each cardiac myocyte. Indeed, dynamic changes occur within the interstitium that directly contribute to adverse myocardial remodeling after myocardial infarction, with hypertensive heart disease, and with cardiomyopathy.71 For example, prolonged pressure overload often results in significantly increased collagen accumulation between individual myocytes and myocyte fascicles.72 The accumulation of ECM and myocardial fibrosis is directly associated with increased myocardial wall stiffness, which in turn causes the poor filling characteristics in diastole that characterize early
stages of heart failure. In contrast to pressure overload, eccentric hypertrophy from volume overload results in a much different pattern of ECM remodeling. In large-animal models of volume overload produced by chronic mitral valve regurgitation, the LV remodeling process is accompanied by a distinctive loss of collagen fibrils surrounding individual myocytes.73 In eccentric hypertrophy, increased ECM proteolytic activity likely contributes to the reduced ECM content and support and thereby facilitates the overall ventricular dilatory process.71

The matrix metalloproteinases (MMPs) and the endogenous tissue inhibitor of metalloproteinase inhibitors appear to play a major mechanistic role in controlling remodeling of the ECM. For example, mice with global deletion of MMP-9 develop normally in the absence of pathophysiological stress, but they show a reduction in the degree of ventricular dilation and adverse matrix remodeling after myocardial infarction.74 Similarly, MMP-2–null mice exhibited a reduction in the rupture rate after myocardial infarction.75 Interestingly, pressure overload induced by aortic constriction in MMP-2–null mice showed blunting of the hypertrophic response.76 Thus, gene deletion of either MMP-9 or MMP-2 was associated with significant effects on myocardial matrix remodeling and whole organ geometry. These findings supported a mechanistic role for both MMP-2 and -9 in adverse myocardial remodeling processes.

Cell Death

Cell death is an important mechanism in the development of heart failure and has been reviewed extensively elsewhere.77 The apoptosis signal-relating kinase appears not to directly regulate cardiac hypertrophy but instead alters cell death and propensity to failure in the setting of hypertrophy.78 Similarly, the BH3 proteins of the Bcl-2 family, Nix, Bnip3, and Puma, promote cell death in the context of hypertrophy.79,80 Underlying the importance of cell death in ventricular remodeling and failure. Protein quality control and degradation appear very important for autophagic cell death and hypertrophy.81

Concluding Remarks

As briefly discussed here, remodeling is a complex phenomenon composed of both adaptive and maladaptive responses of cardiomyocytes and surrounding support cells. Advances in molecular biology and use of genetically modified mouse models have allowed us to elucidate effectors and signaling pathways that contribute to or blunt various aspects of ventricular remodeling (Figure 3). We realize that a large number of important molecular effectors were not discussed in this brief review because it was only our intention to highlight a select group of those effectors that were more recently identified or that are consistent with the theme at hand. We also selected those signaling effectors that provocatively suggest novel therapeutic approaches for translation in the near future, especially those with known pharmacological antagonists.

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References


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