Published in final edited form as:
Circulation. 2010 December 21; 122(25): . doi:10.1161/CIRCULATIONAHA.110.942268.

Molecular pathways underlying cardiac remodeling during pathophysiologic stimulation

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Keywords

Heart failure; hypertrophy; transgenic mice

Overview of cardiac remodeling

The heart is a dynamic organ capable of cellular and ventricular chamber remodeling in response to pathologic and physiologic stimulation. These different stimuli involve extrinsic signals in the form of neuroendocrine agonists and growth factors that are transduced through membrane bound receptors on cardiac myocytes, as well as intrinsic stress sensing associated with mechanical stretch. Intracellular signal transduction cascades then transmit these stimuli throughout the cytoplasm and nucleus to alter cardiac gene expression, metabolism, protein turnover, and contractile function during the remodeling process. Over the past 2 decades the use of genetically engineered mouse models has suggested nodal molecular regulator factors that mediate ventricular remodeling and the transition to heart failure with sustained pathophysiologic stimulation. Here we will highlight emerging concepts in cellular and ventricular remodeling and the more recent molecular signaling pathways that mediate these processes leading to disease, thereby suggesting novel therapeutic targets.

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[1]. Although the term "cardiac remodeling" was initially coined to describe the prominent changes that occur following myocardial infarction[2], [3], it is clear that similar processes transpire following 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 etiologies 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.

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Disclosures

None

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Cardiac hypertrophy is classified as “physiological” when it occurs in healthy individuals following 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 though, 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.

Pathologic remodeling

In addition to ventricular remodeling, pathologic cardiac hypertrophy involves cellular and molecular remodeling such as myocyte growth without significant proliferation, re-expression of fetal genes, alterations in the expression of proteins involved in excitation–contraction (E-C) 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.

Macroscopically 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[4]. Similarly, in volume overload hypertrophy, the internal radius of the ventricle increases, resulting in eccentric hypertrophy[5]. In contrast, pressure overload stress usually produces increased left ventricular wall thickness without or with little increase in chamber size, in a process called concentric hypertrophy (Figure 1A).

Whole organ remodeling and hypertrophy is 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[6]. For example, following myocardial infarction cardiomyocyte length and width are increased, while 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[7].

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). Yet, the adaptive and maladaptive aspects of concentric hypertrophy are still highly controversial[8]. For example a study following patients with increased left ventricular mass and normal left ventricular systolic function for 5 years showed that only 12.3% of patients in the highest quartile of left ventricular mass developed any detectable left ventricular dysfunction, and only 6.9% of these patients developed clinical heart failure[9]. 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, isotonic exercise (swimming and running) has been associated with an increase in chamber dimensions and a proportional increase or no 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[10]. For example, physiological hypertrophy does not induce fibrosis or re-activation of the fetal gene program[11], nor is it a risk factor for arrhythmia, reductions in cardiac function, or future heart failure. An interesting question regarding the stimuli inducing “physiological” and “pathological” hypertrophy is whether it’s 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”[12]. 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 (IGF-1) and growth hormone (GH), and is transduced by phosphoinositide 3-kinase (PI3K)/Akt signaling[13]. Growth factors such as IGF-1 and insulin bind to their membrane-bound tyrosine kinase receptors and activate a 110-kDa lipid kinase PI3K subgroup Iα (p110α). 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 (PDK1), to the cell membrane. This colocalization leads to phosphorylation and activation of Akt.

The central role of the IGF-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, while dominant-negative PI3K resulted in mice with smaller hearts[14]. The increase or decrease in heart size was associated with 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[14]. 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[15]. Consistent with these results, cardiac-specific deletion of the IGF-1 receptor blocked exercise-induced cardiac hypertrophy[16].

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[17, 18]. However, expression of Akt conferred protection from ischemia-induced cell death and cardiac dysfunction, while overexpression of a nuclear-targeted isoform of Akt was also cardioprotective at all times and never lead to dysfunction[18, 19]. Akt1 gene-deleted mice weigh approximately 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[20]. Thus, although the actions of Akt are

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complex, the evidence suggests that it has a role in the normal growth of the heart and adaptive physiologic 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 that next activate the MAPKs. The MAPK cascades are generally sub-classified into three main branches, consisting of p38 kinases, c-Jun N-terminal kinases (JNKs), and ERK1/2[21]. 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 that then recruits the MAP3K Raf-1 to the plasma membrane where it is activated[22]. Other MAP3Ks such as MEKK1 may also be involved in ERK activation under specific conditions[23]. 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[24]. Transgenic mice over-expressing 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[25]. 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 pathologic 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 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 what has been discussed 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 that induce 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[26]. MEK5–ERK5 signaling has been shown to be activated by growth stimuli including serum and ligands for tyrosine kinase receptors and GPCRs. 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 and left ventricular chambers relative to wild-type[27]. 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 TUNEL assays did not suggested 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.

Pathologic hypertrophic pathways (calcineurin and CaMKII)

While some models described above 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 (PP2B). Calcineurin is activated by sustained elevations 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[28]. 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[29]. Cardiomyocytes from calcineurin transgenic hearts are disorganized and markedly hypertrophic with cross sectional areas almost double that of wildtype 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 following pressure overload stimulation or neuroendocrine agonist infusion[30–32].

Another molecule that appears to be central to the pathological hypertrophy response in the heart is Ca^{2+}/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[33]. For example, CaMKII levels are increased and its phosphorylation is elevated after pressure overload in mice[34]. Transgenic mice that overexpress CaMKII developed significant cardiac dilation with reduced function, cardiomyocyte enlargement, and fibrosis[34], suggesting that CaMKII is involved in the pathological response to stress. Conversely, mice with deletion of CaMKIIδ showed either no change in the hands of one group, or reduced hypertrophy following pressure overload stimulation in the hands of another group[35, 36]. However, there is better agreement that mice lacking CaMKIIδ showed reduced propensity to heart failure or secondary pathological effects after pressure overload[35,36]. Taken together, these observations suggest that CaMKII plays a role in the pathological hypertrophy response.

Anti-hypertrophic signaling pathways

Several pathways appear to be anti-hypertrophic or protective, working to counterbalance stress induced remodeling and pathologic changes in the myocardium. Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are re-expressed 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[37]. 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[38]. Importantly, low-salt fed *ANP* null mice exhibit concentric left ventricular hypertrophy despite similar blood pressures with wild-type mice[39]. Mice lacking the ANP receptor (guanylyl cyclase-A) specifically within cardiac myocytes also show enhanced cardiac hypertrophy[40]. 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 anti-hypertrophic actions of ANP on the heart have not been fully elucidated but likely include cGMP-dependent protein kinases (PKG)[41]. For example, transgenic mice engineered to overexpress a catalytic fragment of constitutively active guanylate cyclase of the atrial natriuretic peptide receptor exhibited an increase in intracellular concentration of cGMP and a decreased hypertrophic response to pressure overload or adrenergic stimulation[42].

Nitric oxide (NO) has also been recognized as a negative regulator of the hypertrophic response. The anti-hypertrophic effects of NO are mediated via the second messenger cGMP that then activates PKGI. Studies have suggested that this anti-hypertrophic effect of PKG I is regulated through inhibition of the calcineurin-NFAT signaling pathway[43]. cGMP is catabolized by specific members of the phosphodiesterase superfamily, predominantly by PDE5A. PDE5A was shown to be expressed in the myocardium[44], and PDE5A inhibition in the setting of pressure overload prevents and reverses cardiac chamber, cellular and molecular remodeling[45]. Consistent with previous observations, PDE5A inhibition by sildenafil blunted the activation of ERK and calcineurin-NFAT signaling pathway, suggesting that cGMP anti-hypertrophic activity stemmed from the inhibition of these pathways[45].

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 sarco(endo)plasmic reticulum (SR). T-type calcium channels are re-expressed in adult ventricular myocytes during pathologic hypertrophy[46], although their physiologic 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[47]. Conversely, α1G null mice displayed enhanced cardiac hypertrophy following pressure overload or isoproterenol infusion. Mechanistically, α1G was shown to interact with NOS3, which augmented PKGI activity in the heart after pressure overload stimulation. Thus, re-expressed α1G during pathologic cardiac hypertrophy may bind to NOS3 to provide a local calcium signal to induce its activation, leading to blunted hypertrophy through local cGMP and PKGI.

Another signaling intermediate that can restrain the cardiac growth response to physiologic and pathologic 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[48], demonstrating the anti-hypertrophic and protective properties of Cdc42. Mechanistically, Cdc42 signaled directly to MEKK1 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 anti-hypertrophic signaling mechanism. The anti-hypertrophic 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 following stress stimulation[49]. 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 anti-hypertrophic effect in the heart through NFAT inhibition[50].

Chromatin alterations in cardiac hypertrophic signaling

Many of the kinases and phosphatases discussed above 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 (HATs) p300 and CREB-binding protein (CBP). CBP and p300 are transcriptional coactivators that can cause the relaxation of chromatin structure and promote gene activation. Overexpression of CBP/p300 is sufficient to induce hypertrophy and left ventricular remodeling in transgenic mice, resulting in eccentric left ventricular hypertrophy accompanied by acetylation of cardiac nuclear proteins such as GATA-4 and MEF2 transcription factors[51]. Specific reduction of p300 content or activity diminishes stress-induced hypertrophy and slows the development of heart failure[52]. In agreement with these observations p300 transgenic mice showed significantly more ventricular dilation and diminished systolic function after myocardial infarction than wild-type mice[53].

Histone deacetylases (HDACs) also remodel chromatin, but instead are thought to generally repress gene expression and commensurately alter the cardiac hypertrophic response[54]. HDACs are a large group of enzymes that can be divided into three 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 HDAC9 or HDAC 5 showed enhanced hypertrophy in response to pathological stimuli, suggesting that class II HDACs are antihypertrophic modifiers[55]. In contrast, class I HDACs are considered to play a pro-hypertrophic role[56]. The sirtuins are unique in that they require nicotinamide adenine dinucleotide (NAD) 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 hypertrophic 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 re-expression of fetal genes, alterations in the expression and of proteins involved in excitation – contraction (E-C) 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]. While we will not attempt to review this entire subject, we will highlight a few molecular targets involved in this process. Protein kinase Cα (PKCα) may be one such regulator that alters calcium handling in the heart and leads to greater decompensation and heart failure. In the mouse heart activation of PKCα suppresses SR calcium cycling by phosphorylating protein phosphatase inhibitor 1, leading to reduced activity of SERCA2 by rendering phospholamban less phosphorylated[59]. Conversely, hearts of *Pkcα* deficient mice were hypercontractile and showed increases SR calcium loads and increased phospholamban phosphorylation[59]. *Pkcα* 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 decompensation. Similarly short-term pharmacological inhibition of the conventional PKC isoforms (includes PKCα) significantly augmented cardiac contractility in wild-type mice and in different models of heart failure in vivo, but not in *Pkcα*-deficient mice[60], [61]. Collectively these results suggest that PKCα 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 co-localizes and interacts both with the SERCA2/phospholamban complex and modulates both systolic and diastolic RyR2 function and cardiomyocyte SR 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 left ventricular function following 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 micro-ischemic 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 (during decompensation)[66]. Vascular endothelial growth factor (VEGF) is an endothelialcell 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 extracellularstimuli[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[66]. 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[66]. 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 HIF1A ubiquitination and degradation is reversed by the activation of PKB/Akt and independent of Mdm2[70].

Changes in the extracellular matrix

Ventricular and cellular remodeling in the heart also involves changes in the extracellular matrix (ECM) and associated collagen network that surrounds each cardiac myocyte. Indeed, dynamic changes occur within the interstitium that directly contribute to adverse myocardial remodeling following myocardial infarction (MI), 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 characterizes 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 metal oproteinases (MMPs) and the endogenous TIMP 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 MI[74]. Similarly, *MMP-2* null mice exhibited a reduction in the rupture rate following MI[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 (ASK1) 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 be very important for autophagic cell death and hypertrophy[81].

Concluding remarks

As briefly discussed here, remodeling is a complex phenomena 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, as it was only our intention to highlight a select group of these 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 pharmacologic antagonists.

Acknowledgments

Acknowledgements

None

Sources of funding

This work was supported by grants from the NIH, the Fondation Leducq, and the Howard Hughes Medical Institute (J.D.M.). I.K was supported by a grant from the Human Frontiers Science Program.

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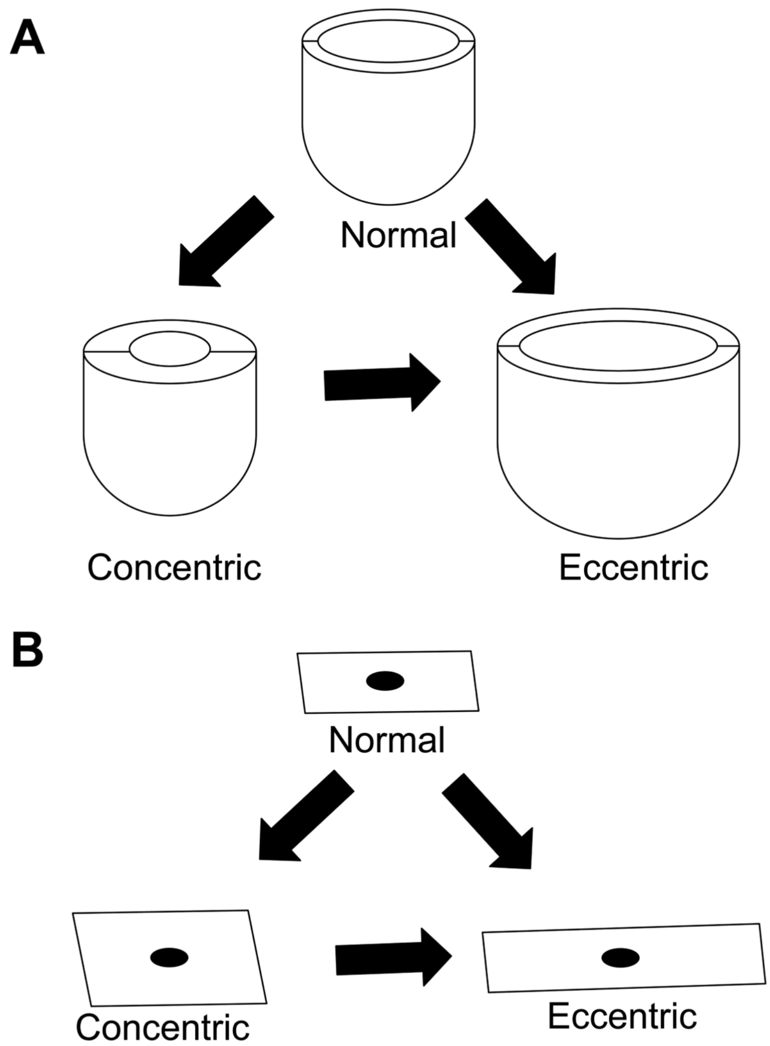

Figure 1.
Macroscopic and microscopic patterns of hypertrophy. (A) Macroscopically the heart can respond to stress by concentric hypertrophy with increased left ventricular wall thickness without an associated increase in chamber size, and eccentric hypertrophy in which the internal radius of the ventricle increases to a greater degree than wall thickness (top). (B) The macroscopic patterns of hypertrophy are usually associated with similar changes in cardiomyocytes. Concentric hypertrophy is characterized by assembly of contractile-protein units in parallel, resulting in a relative increase in the width of individual cardiac myocytes, while eccentric hypertrophy is characterized by assembly of contractile-protein units in series, with a relatively greater increase in the length of the myocyte (bottom). It should be noted that the normal heart and myocyte can develop both patterns of hypertrophy, and that concentric hypertrophy can switch to an eccentric pattern.

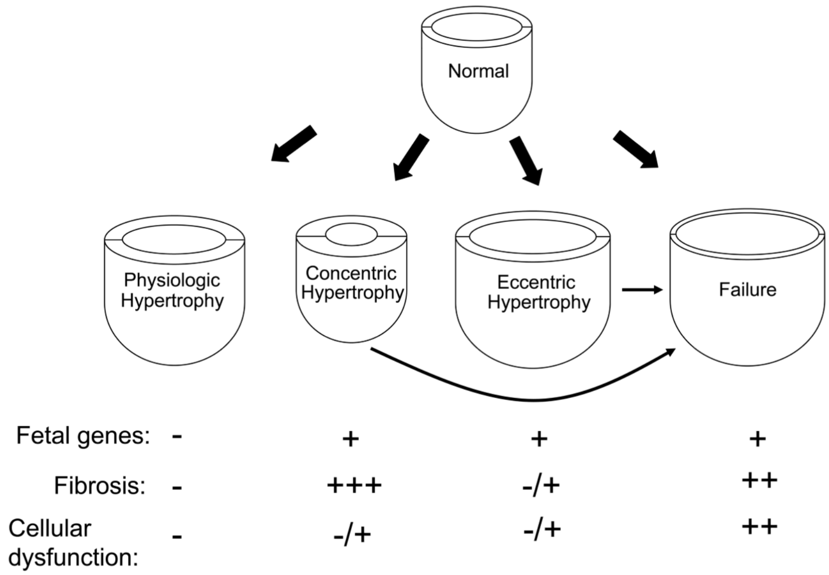

Figure 2.
Ventricular remodeling patterns. Ventricular remodeling can be roughly classified based on geometric shape changes and the pathological or physiologic stimuli that evoke the changes. Exercise usually results in a physiological hypertrophy typified by the lack of fibrosis and the absence of fetal gene expression and chamber growth that is matched with wall and septal thickness growth. Pressure overload usually results in concentric hypertrophy, usually accompanied by fibrosis. Volume overload usually results in eccentric hypertrophy, and is associated with mild or no fibrosis. Except for physiologic hypertrophy, all other types of hypertrophic remodeling can progress to failure and dilation with dysfunctional myocytes.

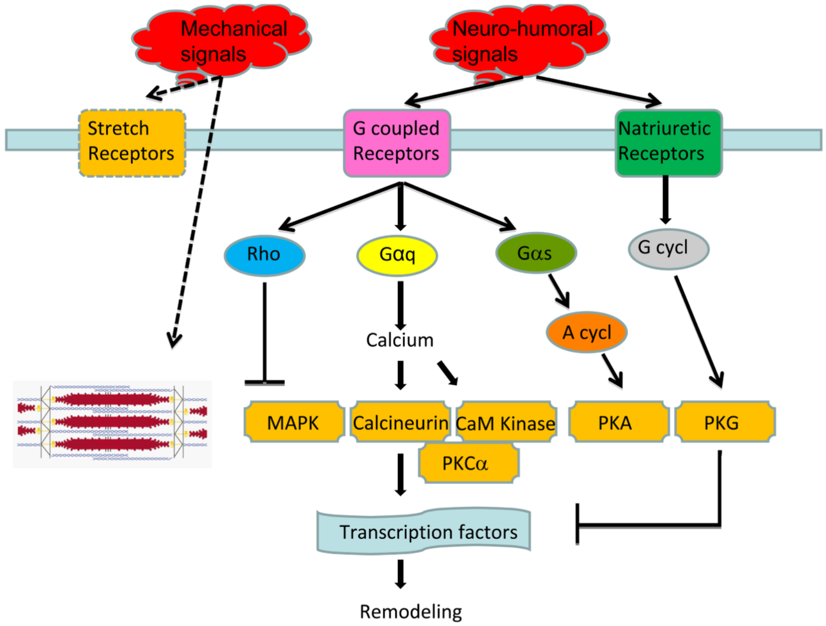

Figure 3.

Simplified diagram of key pathways involved in cardiac remodeling. Neurohumoral stresses are sensed by the membrane-bound receptors, while mechanical stresses are probably sensed by both membrane and sarcomeric stretch-activated mechanisms. These receptors signal through G proteins such as Gαq, Gαs, and Rho family members resulting in modulation phospholipase C, adenylyl and guanylyl cyclases to directly control downstream signaling effectors such as kinases and phosphatases. Calcineurin is a key transducing phosphatase, while kinases such as CaMKII and MAPK appear to have a role in cellular growth, and PKG I appears to have an anti-hypertrophic role. Adenylyl cyclase and PKA also regulate myocyte contractility along with PKCα. These signals culminate in altered transcription that includes the re-induction of the fetal gene program and new cellular growth.