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Physiological myocardial hypertrophy: how and why?

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1. ABSTRACT

Cardiac hypertrophy is defined by augmentation of ventricular mass as a result of increased cardiomyocyte size, and is the adaptive response of the heart to enhanced hemodynamic loads due to either physiological stimuli (post-natal developmental growth, training, and pregnancy) or pathological states (such as hypertension, valvular insufficiency, etc). The mechanisms leading to hypertrophy during pathological and physiological states are distinct but, in general, evidence indicates that hypertrophy results from the interaction of mechanical forces and neurohormonal factors. Hemodynamic overload creates a mechanical burden on the heart and results in stretch of the myocyte and induction of gene expression of cardiac growth factors. Insulin-like growth factor 1 (IGF1) has recently been shown to be the most important cardiac growth factor involved in physiological hypertrophy. In this review, IGF1 and the pathways it triggers will be discussed.

2. INTRODUCTION

In contrast to embryonic developmental myocardial growth, which occurs through hyperplasia (increase in cell number), postnatal growth of the heart occurs primarily through hypertrophy (increase in cell size) (1, 2). Increased myocardial mass as a result of normal postnatal growth, exercise training and pregnancy is referred to as 'physiological' hypertrophy. Molecularly distinct from this type of heart growth is 'pathological' hypertrophy, which occurs as a response to injury and stress signals in states of pressure overload, such as hypertension, and volume overload, such as valvular heart diseases.

The effects that growth stimuli produce are comparable in many cell types and can be broken down into two main phenotypic endpoints: 1) quantitative effects on increasing the level of constitutive proteins (above all

sarcomeric proteins in the case of the heart); and 2) qualitative changes in the gene program (modulating towards either an adult or a fetal gene program type).

The pathological response of the heart to stress signals has three basic phenotypical characteristics: 1) re-expression of fetal-type genes (an event correlating with cardiac failure), i.e.: beta-myosin heavy chain (beta-MHC), atrial natriuretic peptide (ANF), and skeletal alpha-actin (SkAc); 2) histological alterations such as interstitial fibrosis, cell drop-out, and inadequate growth of the cardiac vasculature; and 3) contractile dysfunction (diastolic and/or systolic) (3, 4). Moreover, pathological hypertrophy triggers a transition in the heart from an oxidative toward a more glycolytic metabolism characteristic of the fetal stage (2). Functionally, this type of hypertrophy is initially beneficial in overcoming adverse hemodynamic load in that it maintains cardiac output by increasing ventricular wall thickness as dictated by the Law of Laplace, and is recognized as an adaptive response. This outcome, however, is only a short-term solution and with the persistence of the pathological stimulus, the initial "adaptive" response leads to impaired ventricular relaxation and filling, and, in many cases, progresses to cardiac failure (5).

Contrasting with pathological hypertrophy is that occurring in the healthy individual during postnatal growth, pregnancy, and training. In these cases, hypertrophy is characterized by enhanced cardiac function, normal sarcomere organization, and a normal pattern of cardiac gene expression (6) without interstitial fibrosis or increased cell death. Importantly, vessel growth is maintained at adequate levels (7). Moreover, physical exercising can possibly reverse molecular and functional abnormalities of pathological hypertrophy with or without decreasing ventricular mass, indicating that the two processes are qualitatively distinct (8). In fact, physical training protects against cardiovascular disease, and the resultant cardiac hypertrophy is usually beneficial (8). Moreover, exercise training in heart failure after myocardial infarction enhances cardiac performance and aerobic exercise capacity and reverses pathological hypertrophy and remodeling both in experimental models and in patients (9). Thus, from a pathophysiological standpoint, the consequences of physiological and pathological hypertrophies are profoundly different.

A multitude of studies have focused on pathological growth of the heart, mainly because of the importance of this process in the clinical setting. In fact, pathological hypertrophy is a major predictor of progressive heart disease (10) and, thus, is responsible for the leading cause of hospitalizations and mortality worldwide. Relevant to this, a series of recent studies has shown that pharmacological or genetic blockade of pathological cardiac signaling preserves cardiac function, pointing to the potential efficacy of antihypertrophic therapeutic strategies in the setting of pathological cardiac hypertrophy (11-13). Less is known about the processes leading to physiological cardiac hypertrophy. However, several recent reports have revealed the fundamental importance of the insulin growth factor 1 (IGF1)/phosphatidyl-inositol 3-kinase (PI3K)/Akt pathway for this phenomenon. This will be discussed in following sections.

3. WHY

3.1. Insights from the pathological setting

Starling paved the way for modern research in cardiovascular hemodynamics when he published his Law stating that increases in end-diastolic volume increase the ability of the ventricle to do work (Figure 1, top) (14). Thus, the energy released during contraction depends upon the initial length of the muscle fiber: the greater the heart is stretched by filling, the greater the energy released by contraction. This phenomenon is now thought to be attributed to a change in sensitivity of contractile proteins to Ca^{2+}. However, the conclusion of clinical physiologists that enlargement was a manifestation of the heart calling upon this mechanism to support output from a dysfunctional ventricle seemed at odds with the observation of poorer prognosis in patients with hypertrophy induced by pathological states. This misunderstanding was due to the fact that short-term hemodynamic benefits of dilatation were being highlighted, drawing attention away from the deleterious long-term structural changes.

With the expansion of Laplace's Law to cardiology, heart pathophysiology started to become clearer (15, 16). This law states that ventricular wall stress is directly proportional to cavity size (Figure 1, bottom). Thus, increased chamber diameter and/or blood pressure increase wall stress. In conditions of increased pressure (such as during hypertension and aortic stenosis), normal stress would be regained by increasing ventricular wall thickness (termed concentric hypertrophy); on the other hand, states that increase volume load (aortic and mitral insufficiencies) require an increase in total chamber size and a concurrent increase in ventricular wall thickness to offset the increased wall stress (eccentric-type hypertrophy). This plasticity of the heart is the result of sarcomerogenesis within individual myocytes, which occurs in two modalities: 1) assembly of sarcomeres in parallel arrays increasing cross-sectional area of cells and consequently determining an increase in ventricular wall thickness; and 2) synthesis of sarcomeres in series causing elongation of the myocyte and producing an increase in chamber diameter. Therefore, in pressure overload, the hypertrophy encountered is concentric, while eccentric hypertrophy is observed in conditions of volume overload (17-21).

With progression of the disease state, the increase in pressure and/or chamber size is not further offset by additional increases in wall thickness: hypertrophy becomes not compensating and, eventually, manifest heart failure ensues. On this point, Grossman advanced the notion that ventricular hypertrophy is a biological process marked by a mechanical event and consisting in a classical biological feedback loop. The mechanical signal triggers the production of cardiac mass needed to perform the workload, thus producing a new equilibrium and turning the signal off. However, in pathological settings, this

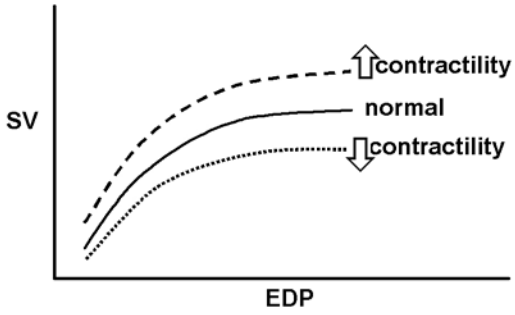

Figure 1. Top: Starling curve showing the relationship between stroke volume and end diastolic pressure (EDP). An increase in end diastolic volume (and, therefore, in EDP since they have an almost linear relationship) causes an increase in stroke volume. The curve shifts up *in situ*ations such as exercise, and down *in situ*ations such as heart failure. Bottom: the Laplace formula: stress is proportional to pressure and volume within the ventricle, and inversely proportional to wall thickness. Therefore, increases in pressure and/or volume of the ventricle can be counteracted by an increase in wall thickness (hypertrophy).

mechanism may not function adequately, and may be either too weak, producing insufficient hypertrophy, or too strong, with a resultant exuberant reaction (22).

Functionally, therefore, pathological forms of cardiac hypertrophy can be identified initially as adaptive responses to increased stress, while a chronic and sustained overload is detrimental to the organism (23). This apparent contradiction for a single response producing a pattern of short-term benefit and long-term harm might seem paradoxical, but is commonly seen in biology.

3.2. Hypertrophy of exercise

During exercise, skeletal muscle requires an increased uptake of oxygen and metabolites and removal of catabolites and heat, the accumulation of which would cause adverse effects. In regularly trained healthy individuals, exercise causes modifications of the ventricular chambers, which result in enhanced cardiac performance via increased stroke volume, contractility, and oxygen consumption (24). Thus, the modifications seen in the heart of athletes are required for sustaining the increase in cardiac output needed to accommodate increased skeletal muscle work. Another important component for exercise is enhanced sympathetic activity to increase heart rate, contractility, and metabolic responses (25).

Two main types of exercise exist. Isotonic or dynamic sports, such as soccer, tend to enlarge the left ventricular internal diameter and wall thickness in proportion so that relative wall thickness is unchanged from normal. Here, the hypertrophy is predominantly eccentric. In contrast, strength-training (isometric) sports, such as weightlifting, produce less increase of the left ventricular internal dimension and a disproportionate increase in wall thickness due to predominantly concentric hypertrophy. In sports with high dynamic and static demands and requiring prolonged training, such as cycling, the hypertrophy is mixed (26). Thus, dynamic exercise is characterized by the need to increase stroke volume to pump more blood, while static exercise is characterized by pressure loading of the heart as a result of increases in intramuscular pressure created by contraction.

3.3. Hypertrophy of growth

Overall growth of an organism is accomplished by changes in the size of individual organs (27). With regard to the heart, there is a striking relationship between workload and ventricular weight across species (28), and as the individual grows from infancy to adulthood, heart size increases proportionally to the increased workload imposed on it. In humans, there is an almost 3-fold increase in cardiac myocyte diameter during development (7). This normal growth process represents a physiological volume overload, similar to its pathological counterpart (19). The wall-to-volume ratio remains relatively constant during development by the proportionate increases in wall thickness and chamber radius, thus maintaining normal wall stress. Importantly, heart growth is also characterized by a proportional growth of coronary capillaries (7).

3.4. Hypertrophy of pregnancy

Significant hemodynamic changes also occur during pregnancy, placing a major burden on the cardiovascular system. During this state, maternal hemodynamics is characterized by altered preload due to plasma and blood volume expansion, and altered afterload, due to the interposition of the low-resistance placental circuit. Thus, gestating women experience a sustained hemodynamic state similar to that of the trained long-distance runner, with the rapid development of eccentric-type hypertrophy. In this way, increased chamber volume and normal wall stress are maintained. Different from athletes, however, contractility seems to be reduced during the late gestation and early post-partum period, and may have important implications for peripartum cardiomyopathy. Hypertrophy during gestation is then self-limiting due to subsequent atrophy secondary to the transient nature of the hemodynamic load experienced (29-33).

4. HOW

4.1. Signaling pathways

The idea that load is the sole determinant of hypertrophy has been challenged from experimental studies and clinical observations demonstrating that neurohormonal factors may be directly responsible (34). The type of factor and, thus, the signaling pathways triggered is related to the type of hemodynamic overload present. Results in humans and animal models have shown that with pressure overload, IGF1 and endothelin 1 (ET-1) are preferentially secreted and the ensuing increased wall stress then stimulates angiotensin II (Ang II) production. In volume load situations, such as in athletes performing mainly isotonic exercise, the sole cardiac growth factor produced seems to be IGF1 (35). Cardiac sympathetic

activation is also important for this type of hypertrophy (35). The overall effect of sympathetic activation is an increase in cardiac output (both venous and arterial) and arterial blood pressure. Enhanced sympathetic activity is particularly important during exercise, emotional stress, and during hemorrhagic shock.

4.1.1. The IGF1-PI3K-Akt pathway

The compensatory mechanisms that lead to myocardial hypertrophy involve alterations in the regulation of signal transduction pathways, as well as control of transcription factors, Ca^{2+}-handling, and energy metabolism. Recent evidence has highlighted signaling molecules regulating the physiological hypertrophy phenotype and, in particular, the IGF1-PI3K-Akt pathway (23). Indeed, compelling evidence shows that signaling molecules play distinct roles in regulating growth in the athlete and diseased heart (35, 36).

IGF1 is characterized by insulin-like short-term metabolic effects and growth factor-like long-term effects on both cell proliferation and differentiation. IGF1 is produced in numerous tissues and particularly by the liver in response to growth hormone stimulation. Interaction of IGF1 (or insulin) with its receptor activates the receptor's cytoplasmic tyrosine kinase activity, which in turn triggers phosphorylation of insulin receptor specific substrates (IRS). Phosphorylated IRSs then interact with cytoplasmic proteins containing src homology 2 (SH2) domains, such as PI3K. Within the target cells, activated PI3K then transduces the functional effects of IGF1, such as enhanced glucose transport, enhanced cardiomyocyte contractility, and the inhibition of programmed cell death (apoptosis).

IGF1 is an important factor in the regulation of postnatal growth and development. In fact, knockout (KO) mouse models of IGF1 or its receptor (IGF1R) have reduced body growth (23). Both IGF1R and insulin receptor (IR) are present in the adult heart and have been shown to be essential for myocardial performance through the action of the PI3K/Akt pathway (37). In athletes, increased cardiac IGF1 production is associated with physiological cardiac hypertrophy (35), and in transgenic (TG) mice overexpressing IGF1R in the heart, physiological cardiac hypertrophy developed with increased myofiber size and enhanced contractile function (38, 39). Cardiac-specific IR KO mice show a decrease in heart size and impaired contractile function (40). Intriguingly, when challenged by pathological hypertrophic stimuli, heart size was increased to a similar extent in both IR KO and wild type (WT) mice, even though IR KO heart size at baseline is smaller than that of WT (41). Thus, while the insulin/IGF1 pathway is involved in physiological hypertrophic growth, its does not appear to be necessary for pathological hypertrophy.

IGF has also protective effects on the heart. Cardiac-specific IGF1 overexpression resulted in less cardiomyocyte death and fibrosis with chronic coronary artery narrowing (42), as well as reduced injury in an *ex vivo* model of ischemia/reperfusion (43). However, although the short-term administration of IGF1 in animal studies has been reported to be beneficial by improving cardiac contractility and counteracting apoptosis, results from clinical trials in which IGF1 was administered chronically have been conflicting (44-46).

The insulin pathway is also a critical regulator of glucose metabolism, promoting its uptake in the heart, glycolysis, and glycogen synthesis as well as inhibiting fatty acid utilization (23).

4.1.1.1. PI3K

PI3K is a member of the lipid kinase family involved in the phosphorylation of membrane phosphoinositides (PIP) (47, 48). PI3K class IA enzymes consist of heterodimeric complexes consisting of a catalytic subunit (p110-alpha, p110-beta, or p110-delta) and a regulatory subunit (p85-alpha, p85-beta, or p55-gamma). This type of class is activated by tyrosine kinase receptors (e.g. growth factor receptors), antigen receptors, and cytokine receptors. In contrast, class IB PI3K enzymes are made up of only the p110-gamma catalytic and the p101 regulatory subunit and are activated by G-protein coupled receptors (GPCRs). There are also three class II PI3Ks (CII-alpha, CII-beta, and CII-gamma), which are thought to be activated by some tyrosine kinase receptors, GPCRs, integrins, and chemokines; and one class III PI3K (Vps34) that appears to be constitutively active.

Physiological hypertrophy involves activation of the PI3K(p110-alpha) pathway, stimulated by receptor tyrosine kinases, whereas pathological hypertrophy utilizes the GPCR-induced PI3K(p110-gamma) pathway (38, 49). Overexpression of a constitutively active (ca) PI3K(p110-alpha) mutant resulted in cardiac hypertrophy *in vivo* to a similar extent to that seen in IGF1R TG mice (50). In contrast, the physiological cardiac hypertrophy obtained by physically exercising mice, as well as in mice over-expressing IGF1R, was completely abolished by co-expression of a dominant negative (dn) PI3K(p110-alpha) or a caPI3K(p110-gamma) mutant (39). Intriguingly, the observed changes in heart size correlated with Akt activity (discussed in the next section) and did not include features characteristic for pathological activation (e.g. reactivation of fetal genes) (38, 51). In addition, it was demonstrated that activation of PI3K(p110-alpha) signaling intervenes in delaying or preventing the progression of the pathological response activated through the GPCR/PI3K(p110-gamma) pathway (38).

PTEN (Phosphatase and TENsin homologue deleted on chromosome 10) antagonizes the activity of PI3K by catalyzing conversion of active inositol lipids into inactive ones. In PTEN KO mice, increased PI3K(p110-alpha) and PI3K(p110-gamma) activity occurred in combination with increased cardiomyocyte size, while cardiac function was depressed (52). This negative inotropic effect was attributed to a decreased cAMP level secondary to inhibition of adenylate cyclase by an uncontrolled PI3K(p110-gamma) activity, whereas the effect on cell size was due to activation of the PI3K(p110-alpha)/Akt pathway. This phenotype, while not affected by a simultaneous deletion of PI3K(p110-gamma), was completely reversed by co-expression of dnPI3K(p110-alpha) (52).

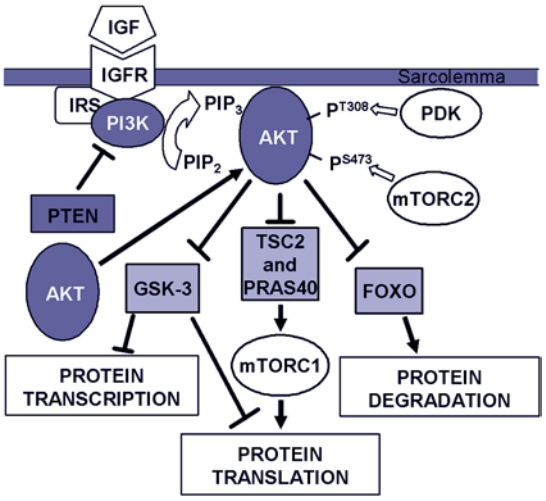

Figure 2. Schematic diagram of the upstream molecules involved in the activation of Akt and the major signaling pathways involved in protein synthesis.

4.1.1.2. Akt

During the last few years, Akt kinase (also called PKB, protein kinase B) has become one of the most comprehensively studied signal-transduction molecules in the regulation of cardiac growth, contractile function, and angiogenesis. Akt is at the crossroad of the IGF1-PI3K-Akt physiological hypertrophy pathway and belongs to the family of serine/threonine kinases. It has 3 isoforms (Akt1, -2, and -3), which regulate a range of downstream targets involved in the modulation of local responses as well as processes concerning metabolism, cell growth, differentiation, survival, and intriguingly, contractile function (23, 47). Akt is activated by IGF1 and insulin through PI3K. The resultant phosphorylated PIP products bind to the pleckstrin domain of Akt and induce its translocation from the cytosol to the plasma membrane where Akt becomes accessible for phosphorylation at T308 by phosphoinositide-dependent kinase-1 (PDK1), which results in its activation (47) (Figure 2). Akt can also be phosphorylated at another regulatory phosphorylation site (S473), but identification of the correspondent kinase has been controversial with numerous previous studies pointing out several putative candidates (53). However, it has been recently suggested that the rapamycin-insensitive complex of the mammalian target of rapamycin (mTORC2) – comprised of mTOR, rictor (rapamycin-insensitive companion of mTOR), and G-beta-L/mLTST8 – is responsible for S473 phosphorylation (54). Akt is activated in response to physical exercise (39, 55) and in caPI3K TG mice, but is repressed in dnPI3K TG mice (50). Once fully activated, Akt migrates throughout the cell to several subcellular organelles and subdomains and phosphorylates specific effector targets (figure 3), a fact that has led to the concept of the importance of Akt re-localization throughout the cell for its correct functioning (47). Akt is eventually deactivated by dephosphorylation at T308 and S473 by protein phosphatase 2A (PPA2) and PH domain leucine-rich repeat protein phosphatase (PHLPP), respectively (56, 57).

4.1.1.2.1. Mice models for studying the role of Akt

Several cardiac-specific mouse models have been used for studying the physiological role of Akt and its upstream molecules *in vivo*. TG mice with specific mutations in either the pleckstrin domain or containing different subcellular localizing signals have been generated. Results from these models have, however, aroused discussion due to the variability of the resulting phenotype. Nevertheless, common results from most models include cardiac hypertrophy and maintenance or improvement of cardiac function. In fact, the Akt E40K mutant, which overexpresses a constitutively active form of Akt, induces a physiological type of hypertrophy together with an improvement in cardiac function (58). The Akt T308D/S473D mutant, which mimics the activated phosphorylation status, is also associated with heart enlargement due to an increase in myocyte size (59). On the other hand, overexpression of myristilated Akt, that confines Akt to the plasmamembrane in proximity to its activator PDK1, was found to be detrimental for cardiac function (60). In addition, overexpression of a nuclear-targeted non-activated Akt is associated with increased contractile function but unaltered heart size: however, cardiac cell size was decreased and cell number increased due to a more dynamic cell cycle progression (61, 62). All together, the studies of the various Akt mutant mouse models imply that the subcellular distribution of Akt activity is a determinant for the resulting cardiac phenotype.

Akt activation is increased 1.5- to 2-fold under physiological conditions in response to exercise training (39) and 6-fold in IGF1 TG mice (43). However, the increase in Akt induction is higher in most of the Akt TG mouse models generated. Therefore, interpretation of phenotypes should always be evaluated keeping in mind that the degree of transgene overexpression often does not correlate with physiological levels. On these premises, Shiojima and colleagues (63) used a tetracycline-regulated system to tightly modulate myristilated myocardial Akt activity. Short-term (2 weeks) activation of myristilated-Akt1 led to compensated cardiac hypertrophy that was completely reversible after transgene expression was turned off. In contrast, sustained activation (6 weeks) determined a higher degree of heart hypertrophy together with contractile dysfunction, increased fibrosis, and decreased capillary density. Therefore, short-term Akt activation or "physiological" activated Akt (similarly to that produced also with the Akt E40K mutant) induces physiological hypertrophy, whereas prolonged Akt activation results in pathological hypertrophy with a drastic increase in heart size. These observations support the notion that activation of the IGF1/Akt pathway may sustain either physiological or pathological hypertrophy, depending on the extent and timing of stimulation.

In KO studies, deletion of a single Akt isoform or a combination of the various isoforms resulted in a number of phenotypes. Global Akt1 KO mice had a reduction in growth (64), while Akt2 KO resulted in insulin resistance and a mild growth delay (65). On the other hand, Akt3 KO

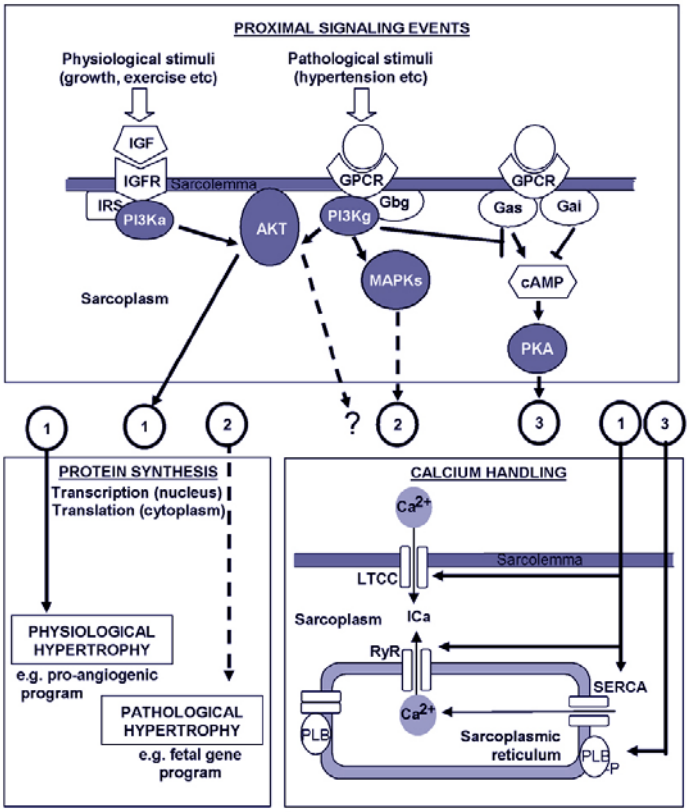

Figure 3. Schematic diagram of the some of the different signaling events involved in physiological and pathological hypertrophy. The PI3K(p110-alpha) (PI3Ka) dependent pathway is responsible for transcription of genes (such as those necessary for formation of new vessels) and increasing calcium-handling in the development of physiological hypertrophy triggered by growth factors (e.g. IGF). Activation of PI3K(p110-gamma) (PI3Kg), through G-protein coupled receptors (GPCR), is antagonistic and triggers various mitogen-activated protein kinase (MAPKs) pathways, which result in protein synthesis of fetal genes, and differential activation of Akt. Moreover, it can be responsible for decreasing contractility through the inhibition cAMP production. Gas: G-alpha s proteins, Gai: G-alpha i protein, Gbg: G-beta/gamma protein; ICa: calcium current.

did not result in growth problems but rather in a reduction in the size of brain cells (66). KO mice harboring combined deletions displayed further phenotypes: Akt1/Akt2 double-KO mice died early after birth, while Akt1/Akt3 double-KO died *in utero* (67, 68). The important role of Akt in controlling cardiomyocytic function has also been explored with a striated muscle-specific KO mouse of the Akt-activator PDK1, which resulted in induction of heart failure (69).

Akt is critical both at baseline and for hypertrophic adaptation in response to physiological stimuli. This has been further addressed using PI3K and IGF1R mouse models. Dn PI3K TG mice displayed a strong response to a pathological stimulus (pressure overload) but a blunted response to a physiological stimulus (training exercise). Similarly, TG mice overexpressing IGF1R in the heart displayed cardiac growth characteristic of physiological hypertrophy (70). In addition, Akt1 KO mice presented with a heart size similar to WT, but showed an extreme hypertrophic response and impaired systolic function when subjected to pressure overload. In response to physical exercise, however, Akt1 KO mice had a blunted hypertrophic response (36). Thus, Akt likely plays a pivotal role in the response to physiological stimuli and in the protection from stress.

4.1.1.2.2. Effects of Akt on Ca^{2+}-handling and contraction

Increased inotropism, lusitropism, and calcium transient are typical features of isolated cardiomyocytes from exercised mice (55), heart failure patients subjected to acute IGF1 administration (71), and mice in which the IGF1/PI3K/Akt pathway has been activated (23). As also discussed in more detail in the article of Kemi OJ *et al.* in the present Issue, contractility in cardiomyocytes is determined by the entrance of Ca^{2+} through the L-type Ca^{2+} channel (LTCC) and release of Ca^{2+} from the sarcoplasmic reticulum (SR) through the ryanodine receptor (RyR). Relaxation is mediated by Ca^{2+} reuptake into the SR through the SR Ca^{2+} ATPase pump (SERCA2). In this process, Akt seems to be involved in the fine-tuning of Ca^{2+}-handling (Figure 3). Indeed, during physical training, Akt is activated and the Ca^{2+} current ($I_{ca,L}$) is increased. In isolated cardiomyocytes, administration of IGF1 results in improved inotropism together with increased $I_{ca,L}$, which is blocked by either specific PI3K inhibitors or LTCC blockers (72). In addition, augmented $I_{ca,L}$ has also been

observed in TG mice overexpressing an active form of Akt, in which cardiac inotropism was improved both *in vivo* (58) and *in vitro* (73). Intriguingly, activation or inhibition of Akt in cardiomyocytes leads to increased and reduced $I_{ca,L}$, respectively, suggesting a role of Akt in regulating LTCC function (47, 74). Similar results were recently obtained in mice deficient for PTEN (74). In contrast, in a mouse model with cardiac-specific nuclear-overexpression of Akt, the observed enhanced contractility was not accompanied by any changes in Ca^{2+} transient or $I_{ca,L}$ (61), suggesting the potential importance of the subcellular location of Akt for its Ca^{2+}-handling effects.

The phenotypic analysis of Akt E40K TG mice revealed a further involvement of Akt in the control of Ca^{2+} cycling in myocytes (58). In fact, active Akt was demonstrated to positively affect SR-Ca^{2+} release/reuptake in association with a marked increase in SERCA2 protein level (58). A similar result was obtained with the nuclear-targeted overexpressed Akt mutant (61) where, however, a decrease in PP1A protein level and an increase of PKA activity was found. In fact, PP1A can specifically dephosphorylate the PKA phosphorylation site of phospholamban (PLB), an inhibitor of SERCA2. Thus, Akt might downregulate PP1A in this model, thereby activating SERCA2. However, the mechanisms by which Akt intervenes in $I_{ca,L}$, SR-Ca^{2+} release/reuptake, and regulation of the SERCA2 protein level remains unknown. These observations concur with molecular and functional responses to exercise in rats (9). A significant increase in SERCA2 protein was associated with enhanced cardiomyocyte contractility and relaxation in the context of either heart failure or the habitual healthy state.

4.1.2. Adrenergic signaling

Catecholamines cause general physiological changes that prepare the body for physical activity (fight-or-flight response). In addition to their induction by acute stress, neurohumoral factors can be induced by mechanical stress (75, 76) and many lines of evidence have suggested their role in increasing cardiac beating frequency and contractility (77, 78), and ultimately, in induction of cardiac hypertrophy (79). Several studies have revealed that an enhanced sympathetic activity selectively confined to the heart is responsible for the physiological hypertrophy in athletes performing predominantly isotonic exercise. However, as pointed out by Neri Serneri (33), this observation is in apparent disagreement with the known increase in vagal tone that also occurs with training. In fact, increased vagal tone is responsible for decreased heart rate, guaranteeing optimum filling and conservation of energy in athletes. In this regard, heart failure patients were reported to have a reduced number of beta adrenergic receptors (ARs) (78) which are uncoupled from Gs proteins (80). Down-regulation of betaARs occurs also with training. Thus, in athletes, there seems to be an uncoupling of inotropy and chronotropy, which permits the simultaneous benefits of increased contraction and decreased heart rate (33).

Catecholamines bind to seven-transmembrane-spanning receptors, which in the heart are present as $beta_1$AR and $beta_2$AR subtypes. Both are coupled to G-proteins, but whereas $beta_2$AR can modulate intracellular signaling through both Gs and Gi proteins, $beta_1$AR is only coupled to Gs proteins. Therefore, because of their distinct G-protein coupling, these two types of receptors have distinct, sometimes even opposite, physiological and pathological roles. The $beta_2$AR-to-G_i pathway promotes a powerful cardiac protective signal that involves G_i, Gbeta-gamma, PI3K, and Akt. In fact, *in vitro* experiments on cardiac myocytes demonstrated that activation of $beta_2$AR-coupled Gi proteins stimulates the PI3K-Akt signaling pathway (81). TG mice overexpressing $beta_1$AR but not $beta_2$AR exhibited heart hypertrophy accompanied by heart failure. In contrast, overexpression of $beta_2$AR restored depressed contractility and prevented the development of pathological hypertrophy in a heart failure model (82) (extensively reviewed in (83)). Through the action of G-proteins, $beta_2$ARs can also stimulate the mitogen-activated protein kinase (MAPK) pathway that leads to the activation of targets involved in the reprogramming of cardiac gene expression (82).

4.2. Protein synthesis

A key element of hypertrophy is the modification of protein turnover. Protein turnover refers to the relative rates of protein synthesis and protein degradation. Typically, contractile proteins turn over every 5 to 10 days. In order for hypertrophy to develop, production of myocardial proteins *de novo* must exceed that of their degradation. This may occur either by increased rate of synthesis or by decreased velocity of degradation. In fact, in the experimental setting of pressure overload, an increase in protein synthesis has been shown to take place primarily through an increase in translation (84). Volume overload, on the other hand, was shown to be due to increased protein degradation, which was responsible for a lower increase in total protein content as compared to pressure overload (85).

4.2.1. Mechanisms increasing protein synthesis

Developmental and hypertrophic stimuli can increase protein synthesis through Akt-induced inhibition of GSK-3 kinase (86). GSK-3 is constitutively active under baseline conditions and is responsible for the shuttling of transcription factors, such as NFATs, GATA-4, and beta-catenin (86, 87) out of the nucleus, thus negatively regulating transcription of genes important for the heart (87). GSK-3 also has an effect at the level of translation initiation in that it phosphorylates eukaryotic translation initiation factor-2B epsilon (eIF-2B epsilon), thereby negatively regulating ribosomal assembly and inhibiting translation (88).

Akt regulates protein synthesis also through GSK-independent mechanisms. The mammalian target of rapamycin (mTOR) is a central controller of cell growth and forms a complex, called mTOR complex 1 (mTORC1, a nutrient- and insulin-regulated complex), when bound to G-beta-L/mLST8 (G-protein beta-subunit-like protein, a regulator of mTOR kinase activity) and raptor (a scaffold protein that functions in recruiting mTOR substrates). Akt has been reported to activate mTORC1 through phosphorylation of tuberin (tuberous sclerosis complex 2, TSC2) and subsequent activation of Rheb (Ras homolog

enriched in brain), a positive regulator of mTOR. However, a recent study has identified PRAS40 (proline-rich Akt substrate 40 kDa) as a dominant-negative effector of mTOR over TSC–Rheb signaling (89). Upon activation of Akt by insulin, PRAS40 is phosphorylated at T246 and binds 14-3-3, a cytosolic anchor protein, which may lead to facilitated release of PRAS40 from mTOR, thereby releasing mTOR from the PRAS40-induced negative regulation. Active mTORC1 then phosphorylates eukaryotic initiation factor-4E (eIF-4E)-binding protein (4E-BP1), which permits the released eIF-4E (the mRNA 5' cap-binding protein) to bind to eIF-4G (a scaffold protein) and eIF-4A (an ATP-dependent RNA helicase), thereby initiating cap-mRNA-dependent translation. Many types of hypertrophic stimuli, including Akt overexpression, Ang II, and pressure overload, have been demonstrated to be sensitive to rapamycin, a compound capable of inhibiting mTOR, leading to an attenuation of induced overgrowth of the heart (90-92), but with little effect on basal protein synthesis (93). This suggests that basal and growth-related syntheses are controlled by different mechanisms. Other studies indicate that mTORC1 plays a role in normal cell growth via activation of the ribosomal protein S6 kinase (S6K). The mechanism, which involves S6K phosphorylation (94), has not yet been fully elucidated, but does not seem important for either pathological or exercise-induced hypertrophic growth (95).

4.2.2. Cardiac remodeling and mechanisms controlling protein degradation

The FOXO (forkhead box-containing protein, O subfamily) transcription factors are known negative regulators of heart growth. In fact, overexpression of FOXO3 produces small-sized myocytes and inhibits growth factor and stretch-induced hypertrophy (96). When located within the nucleus, FOXO factors act as transcription activators of genes involved in proteosomal degradation of proteins, such as atrogin-1/MAFbx (muscle-atrophy F-box) and MuRF1 (muscle-specific ring finger-1) E3 ubiqutin ligases (97). These play a role in the pathophysiology of cardiac hypertrophy and both atrogin-1 (98) and MuRF1 (99) inhibit cardiac hypertrophy by interacting with key hypertrophic signaling pathways. Akt phosphorylation of FOXO promotes its nuclear exit causing inactivation of the transcription of its target genes. Phosphorylated FOXO has been shown to be increased in the heart following pressure overload, insulin treatment, and Akt overexpression. Moreover, once translocated to the cytoplasm, FOXO1, but not other FOXOs, has been shown to bind to and inhibit TSC2, resulting in activation of the mTOR pathway and inhibition of Akt activity through negative feedback on IRS (100).

In addition to their function as transcription activators, FOXOs also have a repressor activity on myocardin-related transcription (101). In this case, the upregulation of a subset of genes involved in heart growth is inhibited.

Apparently opposed to Akt-mediated downregulation of protein degradation during hypertrophy, are recent results suggesting that proteolysis plays an important role in cardiac function and especially in cardiac remodeling. Intriguingly, the ubiquitin proteasome degradation pathway was shown to be upregulated in a mouse model with pressure-induced hypertrophy, particularly in the myocardium submitted to the highest wall stress (102). Moreover, chemically-mediated inhibition of the 26S proteasome prevented the development of pressure overload hypertrophy by phosphorylation of eIF2-alpha that led to downregulation of global protein synthesis. The authors related these findings to the quality control function of the 26S proteasome. The increase in protein synthesis required for cardiac hypertrophy results in an increased quantity of misfolded proteins, and a concomitant increase in protein degradation is necessary for their removal. Proteasome inhibition, therefore, resulted in the attenuation of protein synthesis as an attempt to circumvent the accumulation of aberrant proteins, which would be deleterious for the myocytes. These findings suggest that proteasome activation is not solely involved in mechanism of cardiac atrophy (103) but can also play an important role in promoting increased cardiac muscle mass.

4.3. Angiogenesis

Cardiac remodeling is characterized by alterations in both the myocytes and the extracellular matrix. During remodeling, capillary density together with spatial rearrangement are important determinants for maintaining the balance between myocardial oxygen demand and supply. The processes that cause pathological hypertrophy typically do not increase the amount of blood vessels within the heart to match the thickened heart muscle. As a consequence of the decreased blood flow to the myocardium, the development of heart attacks is common (104). Consistent with this, inhibition of vascular endothelial growth factor (VEGF) in mice subjected to pressure overload resulted in diminished cardiac hypertrophy and promoted progression to heart failure (105). However, TG mice with inducible overexpression of VEGF also showed abnormal vasculature, causing a massive and highly disruptive edema (106). Conversely, the activation of the IGF1/PI3K/Akt pathway in the physiological setting plays an important role in the mechanism of action of physiological cardiac hypertrophy by promoting a coordinated pro-angiogenic program (63, 104, 107). In fact, activation of Akt leads to an induction of VEGF and angiopoietin-2 (Ang-2) expression in an mTORC1-dependent manner (63). Intriguingly, following pressure overload, TG mice overexpressing active Akt maintained better cardiac function and expressed higher levels of VEGF compared to WT (107). However, long-term Akt activation (61) can cause pathological hypertrophy where downregulation of mTOR results in reduced expression of VEGF and Ang-2.

Noteworthy, the process of new blood vessel formation is also associated with remodeling of the extracellular matrix, involving various proteolytic systems such as that of the metalloproteinase (MMP) family. In fact, upregulation of a number of MMPs has been demonstrated to be relevant in models of hypertrophy (108).

5. CONCLUSIONS AND PERSPECTIVES

Understanding the molecular mechanisms underlying physiological heart hypertrophy and the processes involved in the transition from adaptive hypertrophy to heart failure is of great clinical interest. In this review, we have summarized recent knowledge in the understanding of cardiac growth control. Studies of various mouse models have dissected different pathways involved in pathological and physiological cardiac hypertrophy and identified potential targets for the development of novel therapeutic strategies for the treatment of heart disease. The IGF1/PI3K/Akt pathway is critical in modulating cardiac growth, inotropic/luxotropic function, and vasculogenesis, and plays a key role in the development of physiological hypertrophy.

Future studies will provide further insights into the mechanisms and targets of this pathway and possibly identify other important pathways. This will open new possibilities for drug discovery and selective therapeutically applications for modulating cardiac function.

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Abbreviations: IGF: insulin-like growth factor, PI3K: phosphatidyl-inositol 3-kinase, Ang II: angiotensin II, IRS: insulin specific substrate, KO: knockout, TG: transgenic, dn: dominant negative, ca: constitutively active, PIP: phosphoinositide, GPCR: G-protein coupled receptor, PTEN: phosphatase and tensin homolog deleted on chromosome 10, PP: protein phosphatase, mTORC1: mammalian target of rapamycin complex1, LTCC: L-type Ca^{2+} channel VEGF: vascular endothelial growth factor

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