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Phosphoinositide-3 kinase signaling in cardiac hypertrophy and heart failure

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Abstract

Heart failure, a major symptom in the progression of cardiac hypertrophy, is a critical risk factor for cardiac death. A large body of research has investigated cardioprotective mechanisms that prevent or minimize hypertrophy, identifying a variety of specific peptide hormones, growth factors, and cytokines with cardioprotective properties. Recent investigation of the downstream effector pathways for these growth factors has identified molecules involved in the progression of cardiac hypertrophy and heart failure, including phosphoinositide 3-kinase (PI3K), Akt and mammalian target of rapamycin (mTOR). Using genetically modified transgenic or knockout mice and adenoviral targeting to manipulate expression or function in experimental models of heart failure, several investigators have demonstrated that the PI3K-Akt pathway regulates cardiomyocyte size, survival, angiogenesis, and inflammation in both physiological and pathological cardiac hypertrophy. In this review, we discuss the reciprocal regulation of PI3K, Akt and mTOR in cardiomyocytes and their association with cardiac disease.

Keywords

PI3K; Akt; mTOR; cardiac hypertrophy; heart failure

INTRODUCTION

Despite advances in the treatment of cardiac diseases, a cohort study in 2004 revealed that there had been no substantial reduction in the incidence of heart failure in over 2 decades [1]. Cardiac hypertrophy, a major risk factor for heart failure [2], is observed in a wide variety of clinical conditions, including hypertension and aortic stenosis [3, 4]. While cardiac hypertrophy has long been thought to play an adaptive role early in these pathological conditions by reducing wall stress, it is not clear whether it is a necessary protective response [5]. In fact, progressive hypertrophy ultimately becomes maladaptive, transitioning to ventricular dilatation and dysfunction [3, 4]. The functional outcomes classify cardiac hypertrophy as physiological and pathological hypertrophy [6-8]. Physiological hypertrophy resulting from exercise shows adaptive cardiac growth [9], which is also observed during normal postnatal development and pregnancy. Physiological hypertrophy is characterized by preserved contractile function and lack of interstitial fibrosis [6]. On the other hand, while pressure overload initially induces adaptive hypertrophy [10, 11], sustained pressure overload in the left ventricle (LV) eventually results in maladaptive hypertrophy, which is classified as pathological hypertrophy [3, 7, 8]. Pathological hypertrophy is associated with fibrosis and cardiac dysfunction [3, 8]. This hypertrophic

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response is comprised not only of an increase in cell size and protein content, but also complex alterations in gene transcription and translation [7, 8]. Understanding the mechanisms responsible for each of these hypertrophic reactions may help identify novel therapeutic targets to prevent heart failure.

Many years of research dedicated into cardioprotection, has identified a variety of specific peptide hormones, growth factors, and cytokines such as insulin, gp130-dependent cytokines, and insulin-like growth factor (IGF)-I, that can protect the heart from ischemic injury, cardiac hypertrophy, and heart failure [12, 13]. Activation of phosphoinositide 3-kinase (PI3K) and its downstream serine-threonine kinase, Akt (or Protein Kinase B) plays an important role in the cardioprotective effect of the tyrosine kinase receptor signaling pathways [6, 14]. Among the downstream effectors of Akt, mammalian target of rapamycin (mTOR) is particularly well-characterized. Inhibition of mTOR with rapamycin can prevent cardiac hypertrophy, suggesting that mTOR and its downstream molecules regulate development of cardiac hypertrophy [15]. Recent reports revealed that in addition to the rapamycin-sensitive mTOR complex (mTOR complex 1, mTORC1), there is a rapamycin-insensitive complex (mTOR complex 2, mTORC2) [16]. Here, we present an overview of the role of PI3K-Akt-mTOR signaling pathways in the regulation of cell morphology, cell survival, angiogenesis and inflammation in cardiomyocytes in settings of experimental and clinical heart failure.

STRUCTURE AND ACTIVATION OF PI3K, Akt and mTOR

When insulin or IGF-1 binds and activates tyrosine kinase receptors, heterodimers of PI3K are recruited by the SH2 domain in regulatory subunit of PI3K which has high affinity for phosphotyrosine in the receptors [17] (Figure 1). PI3Ks are divided into three classes based on the combination of isoforms of catalytic and regulatory subunits. Class IA PI3K complexes are heterodimers of the α , β or δ isoforms of p110 catalytic domain with the isoforms of the regulatory domain p85 (α , β), p55 (α , γ) or p50 α [17, 18]. Class IB PI3K, also referred to as “PI3K γ ”, is a heterodimer of p110 γ and p101, and is activated by G-protein coupled receptors (GPCR) [18] (Figure 1). All of the class I PI3K phosphorylate PtdIns(4, 5)P₂ to generate PtdIns(3, 4, 5)P₃. Actions of class I PI3Ks is antagonized by tumor suppressor phosphatase and tensin homolog deleted on chromosome ten (PTEN), which dephosphorylates both PtdIns(3, 4)P₂ and PtdIns(3, 4, 5)P₃ [19-21] (Figure 1). Among the class I PI3Ks expressed in the heart, p110 α and p110 γ expression is higher compared to p110 β and p110 δ expression, which is relatively low [22]. Class II PI3K consists of large proteins, 170-210 kDa, which phosphorylate PtdIns and PtdIns4P, however the physiological role of the Class II enzymes remains unclear [23]. Class III PI3K phosphorylates only PtdIns and acts in agonist-independent membrane trafficking processes [17].

Akt contains three isoforms: Akt1 (PKB α), Akt2 (PKB β), and Akt3 (PKB γ). Akt1 and Akt2 are expressed ubiquitously, with high levels seen especially in the brain, heart and lungs [24]. Expression of Akt2 is also observed in brown adipose tissue [25]. Akt3 expression is higher in brain as compared to in the skeletal muscle and liver [26]. PtdIns(3, 4)P₂ and PtdIns(3, 4, 5)P₃ stimulated by growth factors or GPCR in cellular membrane recruit Akt to the plasma membrane from the cytosol, where it is phosphorylated at Thr308 by phosphoinositide-dependent kinase (PDK1) to generate its active form [27, 28] (Figure 1). For full activation of Akt, phosphorylation of Ser473 in a C-terminal regulatory domain is required [29]. Although the mechanism of phosphorylation of Ser473 took many years to reveal, recent reports strongly indicate that a mTOR complex regulates the kinase reaction as discussed below. Activated Akt phosphorylates downstream molecules such as Glucose transporter (GLUT), Glycogen synthase kinase (GSK)-3, and mTOR [14].

mTOR is a large (290 kDa) serine-threonine protein kinase belonging to the phosphatidylinositol kinase-related kinase (PIKK) family [16]. Akt regulates mTOR activation via tuberous sclerosis complex (TSC)-1/2 and Rheb [30, 31]. Phosphorylation of TSC2 by Akt inhibits TSC2 function, disinhibits Rheb, which results in mTOR activation [31]. mTOR exists in two different complex forms usually classified as mTORC1 and mTORC2 [16]. mTORC1, consists of mTOR, Raptor, mLST8/GβL, and PRAS40, and stimulates protein synthesis through p70S6 kinase and eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) in protein translation [32]. Not only does mTORC1 phosphorylate p70S6 kinase, but it also activates eIF4E, a translation initiator. Phosphorylation of p70S6 kinase drives the phosphorylation and activation of S6 ribosomal protein [32], whereas activation of eIF4E leads to phosphorylation and inactivation of 4E-BP1 [33]. mTOR-induced acceleration of protein translation can enhance cell growth and mass [16, 33-35], as seen in osteosarcoma cells, which are enlarged following stimulation by mTOR [36]. mTORC1 is stimulated by amino acid-activated Rag GTPases associated with Rheb [37, 38], and inhibited by rapamycin, a known immunosuppressant. Rapamycin binds with FK506-binding protein (FKBP) 12, and this complex binds specifically to mTORC1 and inhibits its activity [32, 39]. mTOR forms a complex with Rictor, mLST8/GβL and Sin1 to form mTORC2, which stimulates phosphorylation of Akt (Ser473) [16, 40]. PP242, a newly introduced mTORC1 & 2 inhibitor and a member of the family “TORKinibs” (for TOR kinase domain inhibitors), inhibits both mTOR complexes by blocking the ATP-binding site [41, 42].

MECHANISMS OF CARDIAC HYPERTROPHY AND HEART FAILURE

The shift from adaptive (physiological) to maladaptive (pathological) hypertrophy is characterized by multiple pathological changes, including alterations in cell size and survival, angiogenesis and inflammation. The mechanisms underlying each type of hypertrophy and the transition between them are complex and are just beginning to be defined [6]. For studies of the PI3K-Akt signaling pathway in the heart, many gene-targeted and transgenic models have been generated and characterized by multiples groups [43].

CARDIOMYOCYTE MORPHOLOGY

Cardiac hypertrophy is induced by increased myocyte volume which is accompanied by new sarcomere formation in both physiological and pathological forms [6]. The sarcomere is the contractile unit of cardiac muscle [44]. Myocyte enlargement involves acceleration of transcription and translation of mRNA, as well as reduced protein turnover [45]. The ribosomal S6-p70S6 kinase pathway and the S6-4E-BP1-eIF4E pathway are important regulators of translation during the development of hypertrophy, and the activity of these pathways is increased in both physiological and pathological hypertrophy [35, 46]. As described above, both p70S6 kinase and 4E-BP1 are downstream effectors of mTOR [33, 35], suggesting that mTORC1 activity plays a crucial role in regulation of cell size.

In fact, inhibition of mTOR through systemic rapamycin treatment attenuates the hypertrophic response to pressure overload [15, 46]. However, whether long-term treatment with rapamycin is effective for preserving cardiac function in pathological hypertrophy remain undefined. Several groups have reported that thyroid hormone stimulates cardiac hypertrophy in both animals and humans [47, 48]. Tri-iodo-L-thyronine (T3), one of the thyroid hormones, stimulates mTOR activity by activating thyroid hormone receptor, which is co-localized with the p85α subunit of PI3K and stimulates its activity in cardiomyocytes [49]. Recent reports have shown that administration of thyroid hormone can prevent cardiac dysfunction [50, 51]. These findings imply that the effects of thyroid hormone via mTOR, may play an important role in both cardiac hypertrophy and cardioprotection.

CARDIOMYOCYTE SURVIVAL

Cell death of cardiomyocytes is a major factor in pathological hypertrophy which does not occur in physiological hypertrophy [6, 52]. There are three different types of cell death - necrosis, apoptosis, and autophagy [53]. All three types of cell death are present in heart failure [52, 54]. In necrotic cell death, organelles such as mitochondria swell due to the opening of plasma membrane channels that increase influx of extracellular fluid, eventually resulting in failure of the plasma membrane accompanied by inflammation [53]. Apoptosis, which is programmed cell death, involves nuclear atrophy, shrinkage of the cytosol, and loss of mitochondrial membrane potential. Macrophages eliminate cells showing apoptotic shrinkage by phagocytosis without any traces of inflammation [53]. A significant increase in apoptosis is an indication of heart failure [52, 55]. In animals lacking caspase-8 activity, a major mediator of apoptosis, there were fewer apoptotic cells in experimental models of heart failure [56]. Autophagy, which serves to recycle aged organelles and proteins regulated by autophagy-regulated genes (ATG), is also increased in heart failure patients and animal models [53, 57-59]. Autophagy suppresses apoptosis and this mechanism is mediated by mTOR in cardiomyocytes [60]. In addition, several reports have proposed that up regulation of autophagy has cardioprotective effects in heart failure [61, 62]. However, it is still unclear whether the role of autophagy in heart failure is protective or dysfunctional. Recent technical advances may soon elucidate the role of autophagy. LC3, one of the ATGs, acts to select protein for degradation and promote fusion of membrane [63]. Transgenic mice bearing a green fluorescent protein (GFP)-LC3 gene should enable visualization of autophagosomes, making it a useful tool for investigating the mechanisms and effects of autophagy in hypertrophy [64].

CARDIAC HYPERTROPHY AND ANGIOGENESIS

It has been reported that physiological cardiac hypertrophy is accompanied with an increase in myocardial capillary density [65]. Conversely, pathological hypertrophy is associated with a decrease in myocardial capillaries in part by concomitant fibrosis [66]. Decreased myocardial perfusion results in decreased availability of oxygen and nutrients, which leads to an increased risk of heart failure [67]. Therefore, a decrease in myocardial capillaries promotes pathological hypertrophy, leading to heart failure.

Recent studies have suggested that vascular endothelial growth factor (VEGF) secreted from cardiomyocytes plays an important role in cardiac hypertrophy and myocardial infarction [68-71]. It has been reported that Akt and mTOR contributes to angiogenesis by increasing the expression of VEGF and angiopoietin (Ang)-2 [68, 72]. This may be mediated by hypoxia inducible factor (HIF)-1 α , an oxygen-sensing protein that stimulates transcription of VEGF and Ang-2, which can be induced by mTOR [73, 74]. These findings indicate that Akt and mTOR play a crucial role in angiogenesis during physiological cardiac hypertrophy, and suggest that disruption of these signals may promote pathological hypertrophy. However, further studies are required to confirm their role in cardiac angiogenesis and their progression towards pathological hypertrophy.

INFLAMMATION AND CARDIAC FIBROSIS

Although the effects of proinflammatory cytokines such as interleukin (IL)-6, tumor necrosis factor alpha (TNF) α , and IL-1 β are complex [75], increased circulating and intracardiac levels of these cytokines followed by fibrosis are known to be key features of pathological heart failure [76, 77]. The mechanisms underlying the onset of inflammation in human heart failure and animal models such as transverse aortic constriction (TAC) have not been clearly established [78]. TNF α is produced not only by immune cells, but also by cardiac structural cells during pressure overload and ischemia-reperfusion injury [79, 80].

Increased TNF α is believed to have a cardioprotective effect due to activation of manganese superoxide dismutase (MnSOD) and heat-shock proteins (HSPs), however it also contributes to maladaptive responses, including dysfunctional contraction, cardiac hypertrophy, induction of apoptosis, and extracellular matrix (ECM) remodeling [75, 81-85]. Gp130, a component of the IL-6 receptor, suppresses apoptosis and stimulates hypertrophy in cardiomyocytes [86]. However, long-term exposure to IL-6 decreases cardiac contractility [87]. Treatment with IL-1 ameliorates ischemia-reperfusion injury [88] and increases cell size in cardiomyocytes [89]. IL-1 suppresses cardiac contractility in accordance with TNF α and also induces apoptosis [90]. Furthermore, IL-1 regulates ECM remodeling by controlling the proliferation and migration of fibroblasts and collagen synthesis [91].

In addition to these cytokines, several reports have shown association of reactive oxygen species (ROS) with heart failure [92-96]. ROS production is increased in TAC-induced cardiac hypertrophy [92-94]. Furthermore, activity of NADPH oxidase, which produces ROS, is increased in human heart failure [95], suggesting that ROS levels are tightly associated with the inflammatory response during progression of heart failure [96].

One significant difference between physiological and pathological cardiac hypertrophy is fibrosis, which only occurs in pathological hypertrophy and is characterized by increased collagen deposition [4, 97, 98]. Transforming growth factor (TGF) β plays a central role in induction of fibrosis by stimulating the Smad system, which increases expression of collagen types I, III, and VI [97]. In addition to the Smad pathway, TGF β accelerates production of ECM protein by activating TGF β -activated kinase (TAK)-1 [97]. Recently, mouse models of cardiac hypertrophy have exhibited that activation of TGF β signal in non-myocytes stimulates proliferation of non-myocytes and fibrosis in the heart [99]. Additionally, expression of matrix metalloproteinases (MMPs) is controlled by TGF β and proinflammatory cytokines, and disruption of these mechanisms under conditions of pathological hypertrophy induces degradation of ECM [100]. Procollagen type I, the final precursor to collagen type I in the heart, is strongly associated with fibrosis [101] and increased by connective tissue growth factor (CTGF), which is regulated by TGF β [102]. Angiotensin II increases TGF β expression, which enhances fibrosis [103]. Interestingly, angiotensin II-mediated CTGF expression in the heart is enhanced by everolimus, an mTOR inhibitor [104], suggesting that mTOR might inhibit fibrosis by CTGF inhibition. On the other hand, Goraksha-Hicks et al. described PI3K-Akt-mTOR signaling pathway as the Smad-independent pathway of TGF β -induced cellular hypertrophy [105]. Thus, further studies are required to assess the effects of cardiac mTOR on TGF β signaling pathway.

ROLE OF PI3K, Akt and mTOR IN CARDIAC HYPERTROPHY

A number of studies have demonstrated that the PI3K-Akt signaling cascade is associated with cardiac hypertrophy. In dominant negative PI3K transgenic (dnPI3K) mice, exercise-induced physiological cardiac hypertrophy was attenuated compared to WT animals [106]. Interestingly, pathological cardiac hypertrophy induced by TAC in WT and dnPI3K mice had no significant difference [106]. PI3K (p110 α)-dependent hypertrophy was protective in animal models of hypertrophic cardiomyopathy and heart failure [106, 107]. Thus, p110 α plays a crucial role in physiological hypertrophy but not in pathological hypertrophy. Furthermore, inactivation of PTEN, which dephosphorylates PtdIns(3, 4, 5)P₃ produced by PI3K, inhibits cardiac hypertrophy [6, 21, 22]. However, PI3K (p110 γ) deficiency has been shown to protect against isoproterenol-induced heart failure, suggesting that p110 γ mediates pathological cardiac hypertrophy [108]. Consistent with these data, overexpression of either IGF-1 or IGF receptor, activates PI3K (p110 α), and induces physiological cardiac hypertrophy and myocardial infarction [109]. Therefore, results indicate that p110 α

stimulates physiological cardiac hypertrophy, while p110 γ stimulates pathological cardiac hypertrophy.

Akt, a downstream molecule of PI3K, is also involved in cardiac hypertrophy. Even though Akt-deficient and WT mice showed similar heart weight and cardiac function as measured by echocardiography, exercise-induced cardiac hypertrophy was attenuated in Akt-KO mice. The pathological hypertrophic response to pressure-overload was intact, suggesting that Akt mediates physiological hypertrophy rather than pathological hypertrophy [110]. Furthermore, we and other groups previously demonstrated that mice with cardiac-specific overexpression of a constitutively active form of Akt showed significant cardiac hypertrophy, apparently due to increased cardiomyocyte size [111-113]. In transgenic mouse models, prolonged or excess expression of cardiac Akt caused deterioration of cardiac function in models of cardiac hypertrophy or ischemia [68, 114], while moderately activated Akt showed cardioprotection with anti-apoptotic effects against ischemia-reperfusion injury [112]. These findings suggest that Akt alone is not sufficient to protect hearts against cardiac injuries.

mTOR expression has also been found to be associated with the onset of heart failure. mTOR in mRNA and protein levels are elevated in cardiac tissue from heart failure patients compared to healthy subjects [115]. Inhibition of mTOR with rapamycin attenuates cardiac hypertrophy in humans and in animal models [15, 46, 116]. However, transgenic mice with cardiac-specific overexpression of either dominant negative or constitutively active mTOR showed cardiac hypertrophy similar to WT animals following physiological and pathological stimuli [117]. These results suggest that cardiac mTOR has little effect on hypertrophy. The role of mTOR in cardiac function during pathological hypertrophy was fully determined recently. A study in cardiac-specific mTOR deficient mice suggested that cardiac mTOR is necessary to preserve cardiac function under LV pressure overload [118]. The report also showed that 4E-BP1, a downstream effector of mTOR, plays an important role in cardiac function [118]. Recently, we generated cardiac-specific transgenic mice overexpressing wild-type mTOR and observed protection of cardiac function under LV pressure overload [115]. In these animals, TAC-induced interstitial fibrosis and increases in IL-1 β and IL-6 were significantly attenuated compared to WT animals [115]. These data indicate that mTOR is protective against heart injury, and acts by suppressing the inflammatory response [115]. Previously, it was reported that rapamycin increased production of proinflammatory cytokines via NF- κ B, and suppressed anti-inflammatory cytokines via STAT3 [119]. In addition, deletion of TSC2, inhibits mTOR, and suppresses the inflammatory response following lipopolysaccharide (LPS) - or bacteria-induced inflammation [39, 119, 120]. Consistent with a protective and anti-inflammatory role for mTOR, inhibition of mTOR increased mortality in the endotoxin shock model with an accompanying increase in plasma IL-1 β [121]. Rapamycin was first identified as an immunosuppressor and used for the prevention of allograft rejection [122], suggesting that mTOR is pro-inflammatory. However, recent studies suggest that mTOR plays an important anti-inflammatory role based on the stimuli or the tissue.

CLINICAL ASPECTS

There are many effective pharmacological therapies for heart failure, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β -adrenergic receptor blocker, diuretics, antithrombotic agents and vasodilators such as nitric oxide (NO) donors [123, 124]. Numerous clinical studies and meta-analysis have demonstrated that mono therapy or combination therapy with these drugs significantly improve symptoms and increase survival [6, 123, 124]. According to Laughlin et al., the risk of cardiovascular disease is increased in patients showing lower plasma IGF levels [125]. Replacement

therapy with IGF or administration of activators of this pathway may contribute to physiological hypertrophy, and provide protection against subsequent cardiac injury. The data we have summarized in this review strongly suggest that the PI3K-Akt-mTOR signaling pathway activated by IGF-1 is a potent therapeutic target for treatment of cardiac hypertrophy and heart failure. Activation of this pathway is likely to counteract fibrosis and cell death apoptosis, thus preserving cardiac function. On the other hand, mTOR inhibitor rapamycin was introduced as a potential therapeutic agent against cardiac hypertrophy [15, 46]. As discussed above, recent reports including ours suggest that inhibiting cardiac mTOR deteriorates cardiac function in pressure-overload induced cardiac hypertrophy [115, 118]. Therefore, further studies are required to assess the beneficial effects of rapamycin for patients with cardiac hypertrophy.

CONCLUSION

Therefore, accumulated evidence strongly suggests that the PI3K signaling pathway plays an important role in controlling hypertrophic change and preserving cardiac function during the progression of heart failure in cardiac hypertrophy. However, developing effective therapeutic approaches based on these findings is difficult, due to the diverse downstream effectors of PI3K signaling and the multiple pathophysiological features of pathological hypertrophy. Recent data with advanced pharmacological and molecular techniques has revealed critical factors underlying the pathogenesis of cardiac hypertrophy leading to heart failure, including cell death, angiogenesis and inflammation. Hence, it would take additional research to find effective strategies to target the pathogenesis. To find effective strategies to target these processes, we must evaluate optimal duration, timing and dose of pharmacological and molecular agents that control activation of cardiac PI3K signaling.

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Figure 1. Signaling pathway of PI 3-kinase, Akt and mTOR

Signaling pathways are depicted schematically. FKBP: FK506-binding protein, GLUT: glucose transporter, GPCR: G protein-coupled receptor, GSK: Glycogen synthase kinase, IGF: Insulin-like growth factor, PDK: phosphoinositide-dependent kinase, PI3K: phosphoinositide 3-kinase, PtdIns: phosphatidylinositol, PTEN: phosphatase and tensin homolog deleted on chromosome ten, p70S6K: p70S6 kinase, TSC: tuberous sclerosis complex, eIF4: eukaryotic initiation factor 4.