REVIEW

Departments of Anatomy[1], and Immunology[2], College of Basic Medicine, Jiamusi University, Jiamusi; Department of Orthopedic Surgery[3], College of Medicine, Tsinghua University, Beijing, P. R. China

The role of regulation of PTEN gene in signal transduction pathways related to cardiac hypertrophy and chronic heart failure

E. Agbo[1], M-X. Li[1], Y. Zhao[1], R.O. Saahene[2], J-P. Zhao[1], N-J.R. Mbori[3], X.Sun[1,2], G-Z. Tian[1,*], Y-Q. Wang[1]

Received May 11, 2018, accepted May 31, 2018

**Corresponding author: GuoZhong Tian, PhD, College of Basic Medicine, Department of Anatomy, Jiamusi University, No. 148 Xuefu Street, Jiamusi 154007, P. R. China*
858459001@qq.com

Pharmazie 73: 427-432 (2018) *doi: 10. 1691/ph.2018.8531*

This review focuses on the current and past state of understanding with regards to the function of PTEN gene in signalling pathways in chronic heart failure and cardiac hypertrophy and explores how PTEN signalling is modified in the same. The role of PTEN in both pathological and physiological cardiac hypertrophy and how regulation and dysregulation contribute to chronic heart failures and cardiac hypertrophy are also discussed. The modulation of transduction pathway by PTEN with regards to cardiac remodelling, hypertrophy, phenotypic modulation, and apoptosis in both healthy and hypertrophic hearts are talked over. Targeted regulation of PTEN gene in signal transduction pathway forms the basis of development of new PTEN modifying therapies for use in chronic heart failures and related cardiovascular diseases. Signalling pathways are implicated in both pathological and physiological cardiac hypertrophy. These signals involve various protein kinases and activation or inactivation of specific genes that have a role in cardiomyocyte proliferation and apoptosis.

1. Introduction

Although there have been improvements in the management and therapy of cardiac illnesses, an investigation conducted in 2005 established that incidences of cardiac failure have been increasing steadily over a period of the last two decades (Roger et al. 2004). The main hazardous aspect of cardiac failure is heart hypertrophy. Aortic stenosis and hypertension are other mild risks resulting from heart failure (Berenji et al. 2005; Levy et al. 1990).

Whereas it has been deemed that cardiac hypertrophy plays an adaptive function in such pre-mature pathological symptoms by curtailing the stresses on the wall, however, no study has ratified its necessity in protective reaction (Levy et al. 1990; Lorell and Carabello 2000). Indeed, progressive hypertrophy eventually develops into maladaptive, changing into ventricular dysfunction and dilatation. With regards to functionality, cardiac hypertrophy can be categorised in terms of its pathological or physiological effects (Lorell and Carabello 2000). The latter results from growth in cardiac adaptivity which is a common phenomenon in women during pregnancy and postnatal development (Esposito 2002). In contrast, pathological hypertrophy is typified by the inadequacy of interstitial fibrosis and preserved contractile functions (Bernardo et al. 2010; Dorn and Force 2005). Cardiac dysfunction and fibrosis are examples of pathological hypertrophy (Heineke and Molkentin 2006). The hypertrophic reaction is composed of both an upsurge in protein levels, cell sizes, and multifaceted adjustments in translation and transcription of genes (Heineke and Molkentin 2006; Scheuer et al. 1982).

Many medical researchers in the field of cardioprotection have identified a diversity of particular cytokines, growth elements, and peptide genes such as gp130-reliant cytokines, somatomedin, and insulin, which shield the heart against cardiac hypertrophy, heart failure and ischemic injuries (Lorell and Carabello 2000; Gunther and Grossman 1979; Grossman et al. 1975). For instance, the stimulation of phosphoinositide 3-kinase (PI3K) together with variants such as Akt, leads to the stimulation of production of a cardioprotective effect on the receptor signalling pathways by tyrosine kinase (Cantley 2002). The mTOR is an example of a variant or downstream of the PKB. The obstruction of mTOR by rapamycin is known to thwart heart failures, implying that mTOR, in combination with variant molecules can control the progression of cardiac hypertrophy (Frankle and Cantley 1997).

2. Signalling in cardiac hypertrophy

PI3K-Akt pathways have been found to transduce adaptive hypertrophy (Matsui and Rosenzweig 2005; Shioi et al. 2003). The stimulation of the PI3K-Akt pathways, however, does not cause maladaptive hypertrophy (Shioi et al. 2003). The ablation of Phosphoinositide Dependent Protein Kinase 1 (PDPK1) leads to reduced cardiomyocyte growth (Yang and Guan 2007). It has also been found that inactivation of cardiac-specific phosphatase and tension homolog (PTEN) genes result in cardiac hypertrophy (Fruman et al. 1998). The PTEN genes are tumour suppressor phosphatase that dephosphorylates 3' phosphorylated phosphoinositide. This inhibition causes cardiac hypertrophy (Frankle and Cantley 1997). PTEN reduces the amounts of phosphatidylinositol triphosphate (PIP3), a product of PI3K, in myocytes and inhibits cell signalling (Toker and Cantley 1997). The GPCR mediated PI3K-PTEN signalling pathway controls the contractility of the cardiac muscle (Matsui and Rosenzweig 2005).

Akt is the primary intracellular signalling pathway, and it has essential functions in several biological systems such as cell growth, migration, and survival (Toker and Cantley 1997). Research has established that activation of myocardium pathways by methods such as the administration of pharmacological agents or ischaemic post or pre-conditioning is essential for the prevention of reperfused or ischaemic myocardium (Haas-Kogan et al. 1998). The most effective endogenous method of shielding from ischaemic injuries is by performing ischaemic pre-conditioning procedures such as short, non-harmful ischaemic events interposed with reperfusion afore continuous ischaemic episodes (Myers et al. 1998). The aim is to protect the heart by lowering the myocardial infarction. Principally, the protection happens due to the stimulation of the PI3K/

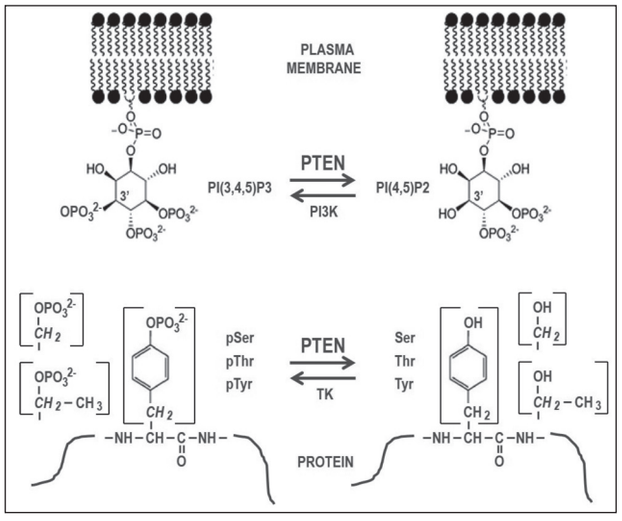

Fig. 1: Schematic representation of PTEN dephosphorylation and reverse catalytic reaction (Pulido 2018).

Akt pathways either at reperfusion after a continuous ischaemic episode, or before the deleterious ischaemic insults (Myers et al. 1998; Pulido 2018). On the other hand, post conditioning achieves significant fortification through Akt deregulation since it involves little ischaemic incidents at the beginning of reperfusion (Pulido 2018).

Usually, various pharmacological agents which stimulate PI3K/Akt signalling pathways have been established to shield the heart from myocardial infarction (Crackower 2002). For instance, atorvastatin, insulin, erythropoietin, glucagon-like peptide, and bradykinin have been demonstrated to lower the number of necrotic cells made in the myocardium at risk after a deleterious ischaemic injury (Vanhaesebroeck 2010). Partly, the shielding is obtained through the activation of PI3K/Akt, further corroborating the proposition that pharmacological regulation and manipulation is significant in preventing the myocardium from experiencing reperfusion-prompted tissue death or harmful ischaemia (Vanhaesebroeck 2010; Coffer and Woodgett 1998). Once Akt has been stimulated, it induces its antiapoptotic features through the phosphorylation of proapoptotic and antiapoptotic substrates (Altomare 1998). The former includes glycogen synthase substrates such as Bad or kinase-3-beta which possess high affinity for the 14-3-3 cytosolic proteins and ultimately becomes inert by bonding them (Shioi et al. 2003; Coffer and Woodgett 1998). Conversely, antiapoptotic substrates include endothelial nitric oxide synthase (eNOS), p70s6 kinase, and mouse double minute (MDM2) which undergo phosphorylation to become stimulate and activate cellular processes necessary for high longevities (Coffer and Woodgett 1998). Nonetheless, protracted stimulation of the pathway might result in malignancy and hypertrophy (Fruman et al. 1998).

PTEN universally exists in normal tissues; its extent of activities depend on its cellular levels, interactions, and localisation with other lipids or proteins (Coffer and Woodgett 1998). The tumour suppressor and the peroxisome proliferator-stimulated γ-agonists are the key molecules which prompt the transcription of PTEN. PTEN regulation is a complicated process which has not yet been entirely understood (Vanhaesebroeck 2010; Coffer and Woodgett 1998). However, phosphorylation is one of the known mechanisms by which the regulation can be inactivated. The primary molecule responsible for the process is CK2 (casein kinase 2) (Altomare 1998). Nevertheless, other kinase-associated enzymes such as threonine protein kinase 11 (LKB1) can phosphorylate PTEN in the in-vitro model (Grossman et al. 1975).

It has been demonstrated that in a phosphorylated condition, PTEN is inert and thus can prevent the degradation of proteasomes (Altomare 1998). On the other hand, PTEN can undergo a reversible inactivation *via* the oxidation prompted by free radical compounds, for instance, ROS (reactive oxygen species) (Coffer and Woodgett 1998). Notably, the ROS which initiates the inactivation process can have various sources. For example, studies have established that insulin induces the stimulation of nicotinamide adenine dinucleotide phosphate oxidase that eventually produces ROS (Coffer and Woodgett 1998). The presence of the latter results in the impediment of PTEN, subsequently activating Akt because of the build-up of PI3P (Stephens et al. 1998). The process of ROS production similarly explains the activity of certain aspects of development that have been demonstrated to retard PTEN regulation. Moreover, experiments have established that the hydrogen peroxide produced within the mitochondria can also impede the moderation of PTEN (Alessi et al. 1997).

3. Mechanisms of heart failure and cardiac hypertrophy

The change from physiological (adaptive) to pathological (maladaptive) hypertrophy is characterised by several pathological shifts such as inflammation and angiogenesis, and cell survival and size (Andjelkovic 1999). The technique for the transition is complicated, thus demanding that each category of hypertrophy is delineated (Alessi et al. 1997; Andjelkovic 1999). In studying the PI3K/Akt cardiac signalling pathway, numerous transgenic and gene-targeted models are generated and characterised by several groups (Stephens et al. 1998).

Increased volumes of myocyte induce cardiac hypertrophy, resulting in a formation of sarcomere in both pathological and physiological states (Manning et al. 2002). The sarcomere represents the unit of contraction of the cardiac muscles (Andjelkovic 1999; Manning et al. 2002). On the other hand, myocyte extension encompasses the acceleration of translation and transcription of mRNA, including concentrated protein turnovers (Garami et al. 2003). The S6-p70S6 ribosomal kinase signalling and the S6-4E-BP1-elf4E pathways are essential controllers of shift as the hypertrophy progresses, and the activities of these signals are augmented in both pathological and physiological forms (Avruch et al. 2006). Notably, both 4E-BP1 and p70S6 are downstream or variant effectors of the mTOR, implying that mTORC1 activity is vital function in analyzing the cell sizes (Garami et al. 2003; Avruch et al. 2006).

When mTOR is suppressed *via* systematic rapamycin treatment, it reduces the hypertrophic reaction to hypertension (Holz et al. 2005). Nonetheless, it does not depend on whether protracted therapy with rapamycin gives positive results in preserving cardiac functions in maladaptive hypertrophy (Hara et al. 2002). Studies have established that thyroid hormones stimulate cardiac hypertrophy in all mammals (Holz et al. 2005). For instance, T3 (Tri-iodo-L-thyronine) hormone activates mTOR activities by stimulating the hormonal receptors co-localised with the p85α subunits of PI3K, as well as actuating cardiomyocyte functions (Fingar et al. 2004). Furthermore, the studies have demonstrated that the thyroid hormones are vital in preventing heart dysfunctions (Fingar et al. 2002). Consequently, it implies that the response of mTOR to the thyroid hormones is significant in both cardioprotection and cardiac hypertrophy.

4. PTEN and reperfusion/ischaemia insult

Research has not yet established the correlation between PTEN levels and reperfusion or myocardial insults (Sancak et al. 2010). For instance, in the field of cancer research, the primary focus is on how PTEN levels can be restored (Fingar et al. 2002; Sancak et al. 2010). In other areas where survival is the main objective, such as carrying out reperfusion/ischaemia in the myocardium because of the benefits of Akt stimulation, the attention is diverted towards the downregulation of PTEN, preferably in a reversible manner (Sancak et al. 2008). Studies have established that ischaemia prompts PTEN activation and phosphorylation as a fundamental defensive technique (Weichhart and Saemann 2009). The stimulation depends on the information acquired on the brain reperfusion (Jacinto et al. 2006). Similarly, low PTEN levels in heart muscles are linked to remodelling and hypertrophy (Weichhart and Saemann 2009). In the same vein, apart from regulating

the contractile and size functions in cardiomyocytes, PTEN also controls the calcium currents in L-type myocytes (Sancak et al. 2008; Jacinto et al. 2006).
Fascinatingly, despite the scarcity of information on the functions of PTEN in cardiovascular pathophysiology, a new study has emphasised the significance of PI3K/PTEN signalling based on the information obtained from other systems in the tissues (Feldman et al. 2009). In other words, manipulating the therapeutic interactions is critical for the longevity of the myocardial cell (Vanhaesebroeck 2010; Feldman et al. 2009). In fact, it has been demonstrated that in other tissue systems, certain growth elements such as insulin increase the survival by impeding PTEN through the localised ROS generation and stimulating the signalling pathways (Janes et al. 2010). The research shows that the defensive effect concerns the impediment of PTEN that makes it easy to use in the critical environment of reperfusion/ischaemia (Oudit et al. 2008).

5. Ischaemic preconditioning

The most effective endogenous defensive mechanism against reperfusion insult is ischaemic preconditioning since it is linked to the stimulation of the PI3K/Akt signalling pathways (Wick 1999). Recent reports indicate that PTEN activities are attenuated by using ischaemic preconditioning (Zak and Rabinowitz 1979). Scientists demonstrated the same by experimenting with a quarantined perfused mouse heart to show that PTEN downregulates after 35 minutes reperfusion and 20 minutes ischaemia (Oudit et al. 2008; Zak and Rabinowitz 1979). Consequently, it is prudential to note the comparison between the test and the data acquired in the ischaemic brain without lowering the significance of the experimental results (Zak and Rabinowitz 1979). In the same vein, it should be noted that the test investigated PTEN in the setting in the context of first time reperfusion/ischaemic insult. It also established that an upsurge in phosphorylation of Akt and PTEN occurred in the hippocampus following a reperfusion injury. This information corroborates the supposition that reperfused or ischaemic PTEN cells downregulate in an endogenous defensive technique (McMullen et al. 2004).

6. Angiogenesis and cardiac hypertrophy

Research has shown that adaptive cardiac hypertrophy is concomitant to an upsurge in myocardial pathway compactness (Ching et al. 1996). On the other hand, maladaptive hypertrophy partly diminishes the myocardial pathways by collateral fibrosis (Bedotto et al. 1989). A decrease in myocardial reperfusion diminishes the availability of supplements and oxygen, eventually resulting in an increased peril of heart failure (Sui et al. 2008). Consequently, reduction in myocardial pathways encourages maladaptive hypertrophy, resulting in heart failure (Gerdes and Lervasi 2010). The endothelial vascular growth factor which the cardiomyocytes produce plays a significant function in myocardial infarction and cardiac hypertrophy. Studies suggest that mTOR and Akt encourage angiogenesis by heightening the expression of angioprotein-2 and the growth factor (Kenessey and Ojamaa 2006). Thus, it is evident that mTOR and Akt are instrumental in angiogenesis throughout adaptive myocardial hypertrophy, and further implying that the disruption of the pathways is likely to spur pathological or maladaptive hypertrophy (Whelan et al. 2010).
Considering the acute functions of PTEN and PKB/Akt in cardiac metabolism coronary angiogenesis, it can be theorised that a reduction in PTEN may spur an early angiogenesis reaction and impede deleterious shifts in the manifestation of the cardiac metabolic chromosomes (Pulido 2018; Hotchkiss et al. 2009). Testing evaluates coronary angiogenesis for CD31 markers for cardiac endothelial tissues (Gerdes and Lervasi 2010). In that regard, it is plausible that vascular rarefaction is the primary determining factor for functional coronary reaction to biomechanical stresses (Hotchkiss et al. 2009).
Since PTEN negatively regulates the PI3K systems and a decrease in PTEN cause protracted PKB/Akt stimulation in the heart, it is plausible that decline in PTEN results in defence against biomechanical stresses (Guerra et al. 1999). In support of the hypothesis, experiments have proved that hemodynamic and transthoracic echocardiographic evaluation confirm a moderate reduction in the systolic functions in mice (Olivetti et al. 1997). The notable reaction to excess cardiac pressure is the growth of maladaptive hypertrophies which, when combined with increased apoptosis and interstitial fibrosis, is concomitant to the stimulation of mitogen-stimulated protein kinase (MSPK) as well as phosphorylation (Wencker et al. 2003).
Biomechanical stress refers to a primary rejoinder characteristic in cardiac diseases (Glick et al. 2010). Studies have established that PTEN is crucial in impeding the growth of maladaptive hypertrophies with the protection of myocardial role in reaction to biomechanical stress (Matsui et al. 2007). Alterations in PTEN expressions in both human and experimental models of heart failures ratify the essence of the same in cardiac diseases (Gurusamy et al. 2009). In cardiovascular systems, PTEN negatively regulates both alpha and beta PI3K isoforms in endothelial tissues, vascular smooth muscles, and cardiomyocytes (Gottlieb and Mentzer 2010; Nakatogawa 2007). The stimulation of Akt by different extracellular activation relies on PI3K functions and controls several facets of cellular functions such as growth, metabolism, angiogenesis, and survival (Mizushima et al. 2004).

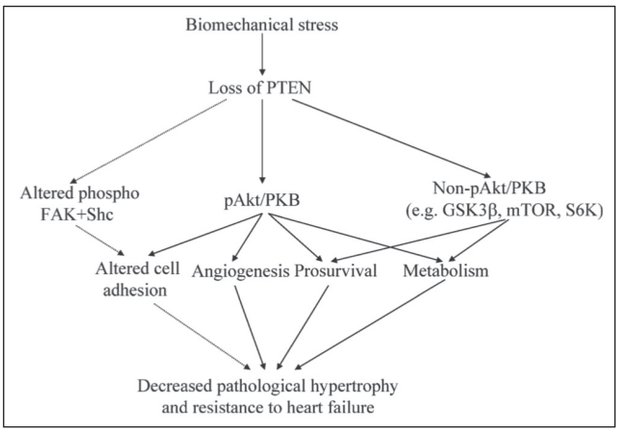

Fig. 2: Representation of the functions of PTEN in the myocardial reaction to maladaptive biomechanical stresses (Oudit et al. 2008).

According to Fig. 2, biomechanical stress initiates the destruction of PTEN, leading to the alteration of focal adhesion kinase and Shc proteins. This leads to the alteration of cell adhesion which results in cardiac failure due to pathological myocyte hypertrophy. The destruction of PTEN also leads to alterations in pAkt activity, increasing the rate of angiogenesis, cell adhesion and pro-survival, while altering metabolism. The activity of non-pAkt such as glycogen synthase kinase 3 beta is altered, leading to the change in cardiac metabolism. The resultant effect of all these processes is the aggressive cardiac hypertrophy which results in heart failure.
Another research finding has shown that simvastatin lowers cardiomyocyte hypertrophy by raising the expression levels of PTEN (Hudlicka et al. 1992). Simvastatin has been established to significantly increase PTEN expression in cultured and spontaneously hypersensitive mice (Gavin et al. 1998). Additionally, administration of PTEN antisense oligodeoxynucleotides considerably prevents the expression of same (De Boer et al. 2003). Consequently, there is a potential cellular pathway caused by the hypertrophic effects of simvastatin in cardiomyocytes, further indicating that simvastatin is a useful pharmacological compound against hypertrophy of cardiomyocytes (Shiojima et al. 2005; Sano et al. 2007).
Statins have been demonstrated to possess excellent fat modulatory ramifications while also preventing the propagation of cardiac fibroblasts in smooth vascular tissues (Tirziu et al. 2007). Hence, they are linked to low incidences of cardiovascular mortality and insults

in patients vulnerable to cardiovascular risks (Heineke et al. 2007). Nevertheless, their effects on the particular cellular mechanism and cardiomyocytes underlying their activities have not been researched (Shiojima and Walsh 2006; Hudson et al. 2002). Conversely, published research has verified that simvastatin lowers the amounts of molecular isoprenoid intermediates and prevents the isoprenylation and tiny cellular mass G-proteins as Rho/Ras, to eventually apply defensive techniques on cardiovascular systems (Zhong et al. 2000; Hedayat et al. 2010). In other words, they are vital in tissue hypertrophy and proliferation through regulating the transformation and expression of Ras proteins across the cell membrane, and the Akt and MSPK transduction pathways are instrumental within the physiological functions of the same (Shioi et al. 1997).

Myocardial fibrosis results from excessive collagen deposition, characterised by an increase in collagen volume and concentration (Baumgarten et al. 2002). Collagen disorder and imbalance, and abnormality of the myocardial interstitial structure are the common maladaptive characteristics of the different kinds of cardiovascular maladies (Gurevitch et al. 1996). Examples of the same include arrhythmia, myocardial infarction, cardiomyopathy, atherosclerosis, viral myocarditis, and hypertension (Wong and Goeddel 1988). The miR-26α are upregulated after infarction in the myocardium (Sharma et al. 1996). Depending on the extent of myocardial fibrosis, miR-26α is known to augment the fibrosis of the myocardial tissues (Sun et al. 2007). Since PTEN belongs to the PTP class of genes, it can locate the transcription product of cardiac hypertrophy (Haudek et al. 2007; Siwiket al. 2000). Furthermore, it dephosphorylates PI3P to antagonise its phosphorylation effects on PI2P, hence inhibiting downstream and Akt signalling pathway stimulation (Yamauchi-Takihara and Kishimoto 2000). Research has demonstrated that PI3K/Akt transduction pathway activation has a significant function in encouraging myocardial fibrosis and in upregulation of matrix metallopeptidase 9 (MMP-9) (Yu et al. 2003).

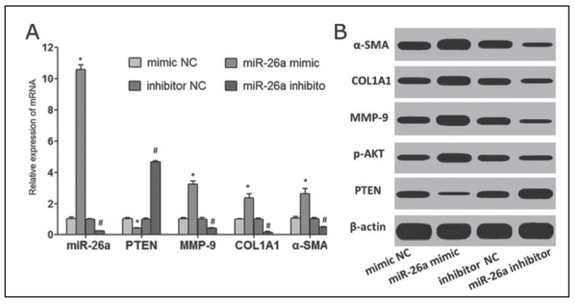

Fig. 3. MMP-9 and miR-26α modulated Akt/PI3K activity expression in hypertrophic cardiac tissues (Zhang and Cui 2018). *A* shows mRNA expressions detected by qRT-PCR. *B* is the protein expressions identified by Western blot method (Zhang and Cui 2018; Aukrust et al. 2005).

7. Clinical aspects

7.1. Cancer

PTEN, a gene tasked with tumor suppression, is either mutated or lost during malignancy. It is estimated that up to 70% of prostate cancer patients lose a copy of the gene before being diagnosed for malignancy. The gene mutates during tumor development leading to its deletion. The subsequent reduction in enzymatic activity leads to increased proliferation of cells and decreased necrosis of apoptotic cells. Some of the other malignancies responsible for PTEN deactivation include endometrial carcinomas and glioblastomas. Decreased gene expression, on the other hand, occurs following malignancies such as lung and breast carcinomas. In addition, PTEN mutation predisposes to carcinogenesis.

7.2. Non-malignant neoplasia

PTEN mutations are not limited to malignancies, as more than 70 mutations have been identified in patients suffering from Kayden syndrome. The resultant effect of the mutation is defective coding which in turn leads to the formation of denatured proteins. Such proteins proliferate uncontrollably with minimal control during the cell cycle. The defective proteins also are non-apoptotic, not responding to stimuli such as those from the p53 gene. Uncontrolled cell growth in turn predisposes to the development of malignancies, especially in fast growing tissues such as the breast, uterus and the thyroid glands. The excessive proliferation also leads to the development of benign tumors such as harmatomas which are characteristic of Cowden's syndrome.

7.3. The function of the brain and autism

Some defects in the PTEN gene are implicated in the aetiology of autism spectrum disorders. The pathogenesis involves the interaction of the defective gene with p53, which is a gene coding for a tumour suppressor apoptotic protein. The p53 protein leads to massive destruction of the defective genetic structures, leading to mitochondrial changes and excessive energy generation within the cerebellum and hippocampal regions. These central nervous system regions are responsible for the regulation of social behaviour, emotions and cognition. Apart from autism, individuals with defective PTEN protein are at risk of developing dysplastic gangliocytomas, which are lesions within the cerebellum.

7.4. Cell regeneration

The strong association of PTEN with cell growth inhibition is being pursued in order to achieve treatment and induce regeneration of stable tissues and cells, such as neurons. The removal of PTEN mutants has been shown to induce regeneration of neural tissue in mice.

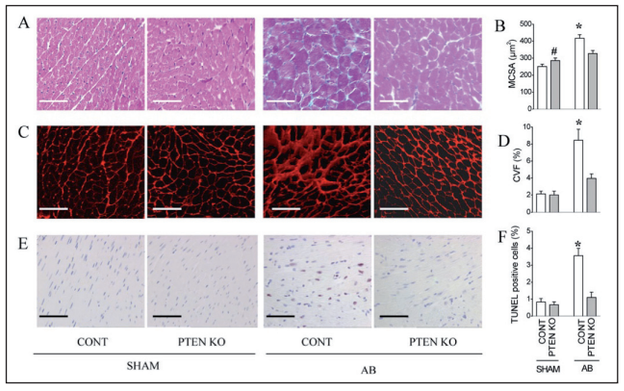

Fig. 4. Reduced interstitial fibrosis, apoptosis, and cardiac hypertrophy in PTEN KO mouse in reaction to eight weeks of overload in pressure (Oudit et al. 2008). *A* denotes trichrome parts; ***B*** represents the cardiomyocyte cross-sectional area (MCSA); ***C*** shows Picrosirius red sections using a confocal microscope; ***D*** represents the collagen fraction by volume; E shows areas affected by apoptosis, and the graphical denotation is shown in ***F*** (Oudit et al. 2008).

7.5. Heart diseases

Maladaptive heart failures and ventricular hypertrophies are attendant to the variation of expression in the genes responsible for the modulation of fatty acids and glucose metabolism (Nishida et al. 2009). The stimulation of the PKB/Akt alters the expression of the metabolic hormones that could encourage the cardiac muscles to handle the maladaptive stimulus (Kostin et al. 2003). Therefore, in the context of maladaptive hypertrophy, a decrease in PTEN levels protects the expression of metabolic genes and cardiac angiogenesis thereby inhibiting the development of heart failures (Glick et al. 2010). On the other hand, high levels of PTEN expressions increase apoptosis in new cardiomyocytes (Cantley 2002).

8. Conclusion

In conclusion, the PTEN-PI3K-Akt-mTOR signalling pathway stimulated by IGF-1 comprises useful curative targets for the clinical management of heart failure and cardiac hypertrophy. Notably, the stimulation of the PTEN genes usually counters cardiac hypertrophy and chronic heart failure, thereby sustaining the functions of the heart. In the same vein, since PTEN genes are negative modulators of the insulin signalling pathways, they are possible targets for enhancing insulin sensitivity in cardiac hypertrophic hearts. It is also worth mentioning that whereas downregulating PTEN could potentially be harmful since it encourages malignancies and unwanted growths, acute PTEN suppression could prove essential in spurring the survival of myocardial tissues after an ischaemic/reperfusion insult.

Acknowledgement: My sincere gratitude to Joyce Massaro for her support by reading over my review article.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

References

Alessi DR, James S.R, Downes CP, Holmes AB, Gaffney PR, Reese CB, Cohen P (1997) Characterization of a 3-phosphoinositide-dependent protein kinase which phosphorylates and activates protein kinase Bα. Curr Biol 7: 261-269.

Altomare DA, Lyons GE, Mitsuuchi Y, Cheng JQ, Testa JR (1998) Akt2 mRNA is highly expressed in embryonic brown fat and the AKT2 kinase is activated by insulin. Oncogene 16: 2407-2411.

Aukrust P, Gullestad L, Ueland T, Damås JK, Yndestad A (2005) Inflammatory and anti-inflammatory cytokines in chronic heart failure: Potential therapeutic implications. Ann Med 37: 74-85.

Avruch J, Hara K, Lin Y, Liu M, Long X, Ortiz-Vega S, Yonezawa K (2006) Insulin and amino-acid regulation of mTOR signaling and kinase activity through the Rheb GTPase. Oncogene 25: 6361-6372.

Baumgarten G, Knuefermann P, Kalra D, Gao F, Taffet GE, Michael L, Blackshear PJ, Carballo E, Sivasubramanian N, Mann DL (2002) Load-dependent and-independent regulation of proinflammatory cytokine and cytokine receptor gene expression in the adult mammalian heart. Circulation 105: 2192-2197.

Bedotto JB, Gay RG, Graham SD, Morkin E, Goldman S (1989) Cardiac hypertrophy induced by thyroid hormone is independent of loading conditions and beta adrenoceptor blockade. J Pharmacol Exp Ther 248: 632-636.

Berenji K, Drazner MH, Rothermel BA, Hill JA (2005) Does load-induced ventricular hypertrophy progress to systolic heart failure? Am J Physiol Heart Circul Physiol 289: H8-H16.

Berk BC, Fujiwara K, Lehoux S (2007) ECM remodeling in hypertensive heart disease. J Clin Invest 117: 568-575.

Bernardo BC, Weeks KL, Pretorius L, McMullen JR (2010) Molecular distinction between physiological and pathological cardiac hypertrophy: experimental findings and therapeutic strategies. Pharmacol Ther 128: 191-227.

Brown JM, White CW, Terada LS, Grosso MA, Shanley PF, Mulvin DW, Banerjee A, Whitman GJ, Harken AH, Repine JE (1990) Interleukin 1 pretreatment decreases ischemia/reperfusion injury. Proc Nat Acad Sci USA 87: 5026-5030.

Brown RD, Jones GM, Laird RE, Hudson P, Long CS (2007) Cytokines regulate matrix metalloproteinases and migration in cardiac fibroblasts. Biochem Biophys Res Comm 362: 200-205.

Cantley LC (2002) The phosphoinositide 3-kinase pathway. Science 296: 1655–1657.

Ching GW, Franklyn JA, Stallard TJ, Daykin J, Sheppard MC, Gammage MD (1996) Cardiac hypertrophy as a result of long-term thyroxine therapy and thyrotoxicosis. Heart 75: 363-368.

Coffer PJ, Jin J, Woodgett JR (1998) Protein kinase B (c-Akt): A multifunctional mediator of phosphatidylinositol 3-kinase activation. Biochem J 335: 1-13.

Crackower MA, Oudit GY, Kozieradzki I, Sarao R, Sun H, Sasaki T, Hirsch E, Suzuki A, Shioi T, Irie-Sasaki J, Sah R (2002) Regulation of myocardial contractility and cell size by distinct PI3K-PTEN signaling pathways. Cell 110: 737-749.

De Boer RA, Pinto YM, Van Veldhuisen DJ (2003) The imbalance between oxygen demand and supply as a potential mechanism in the pathophysiology of heart failure: the role of microvascular growth and abnormalities. Microcirculation 10: 113-126.

Dorn GW, Force T (2005) Protein kinase cascades in the regulation of cardiac hypertrophy. J Clin Invest 115: 527-537.

Esposito G, Rapacciuolo A, Prasad SVN, Takaoka H, Thomas SA, Koch WJ, Rockman HA (2002) Genetic alterations that inhibit in vivo pressure-overload hypertrophy prevent cardiac dysfunction despite increased wall stress. Circulation 105: 85-92.

Feldman ME, Apsel B, Uotila A, Loewith R, Knight ZA, Ruggero D, Shokat, KM (2009) Active-site inhibitors of mTOR target rapamycin-resistant outputs of mTORC1 and mTORC2. PLoS Biol 7: e1000038.

Fingar DC, Richardson CJ, Tee AR, Cheatham L, Tsou C, Blenis J (2004) mTOR controls cell cycle progression through its cell growth effectors S6K1 and 4E-BP1/eukaryotic translation initiation factor 4E. Mol Cell Biol 24: 200-216.

Fingar DC, Salama S, Tsou C, Harlow ED, Blenis J (2002) Mammalian cell size is controlled by mTOR and its downstream targets S6K1 and 4EBP1/eIF4E. Genes Devel 16: 1472-1487.

Fruman DA, Meyers RE, Cantley LC (1998) Phosphoinositide kinases. Annu Rev Biochem 67: 481–507.

Garami A, Zwartkruis FJ, Nobukuni T, Joaquin M, Roccio M, Stocker H, Kozma SC, Hafen E, Bos JL, Thomas G (2003) Insulin activation of Rheb, a mediator of mTOR/S6K/4E-BP signaling, is inhibited by TSC1 and 2. Mole Cell 11: 1457-1466.

Gavin JB, Maxwell L, Edgar SG (1998) Microvascular involvement in cardiac pathology. J Mol Cell Cardiol 30: 2531-2540.

Gerdes AM, Iervasi G (2010) Thyroid replacement therapy and heart failure. Circulation 122: 385-393.

Glick D, Barth S, Macleod KF (2010) Autophagy: cellular and molecular mechanisms. J Pathol 221: 3-12.

Gottlieb RA, Mentzer Jr RM (2010) Autophagy during cardiac stress: joys and frustrations of autophagy. Ann Rev Physiol 72: 45-59.

Grossman W, Jones D, McLaurin LP (1975) Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 56: 56-64.

Guerra S, Leri A, Wang X, Finato N, Di Loreto C, Beltrami CA, Kajstura J, Anversa P (1999) Myocyte death in the failing human heart is gender dependent. Circul Res 85: 856-866.

Gunther S, Grossman W (1979) Determinants of ventricular function in pressure-overload hypertrophy in man. Circulation 59: 679-688.

Gurevitch J, Frolkis I, Yuhas Y, Paz Y, Matsa M, Mohr R, Yakirevich V (1996) Tumor necrosis factor-alpha is released from the isolated heart undergoing ischemia and reperfusion. J Am Coll Cardiol 28: 247-252.

Gurusamy N, Lekli I, Gorbunov NV, Gherghiceanu M, Popescu LM, Das DK (2009) Cardioprotection by adaptation to ischaemia augments autophagy in association with BAG-1 protein. J Cell Mol Med 13: 373-387.

Haas-Kogan D, Shalev N, Wong M, Mills G, Yount G, Stokoe D (1998) Protein kinase B (PKB/Akt) activity is elevated in glioblastoma cells due to mutation of the tumor suppressor PTEN/MMAC. Curr Biol 8: 1195-1198.

Hara K, Maruki Y, Long X, Yoshino KI, Oshiro N, Hidayat S, Tokunaga C, Avruch J, Yonezawa K (2002) Raptor, a binding partner of target of rapamycin (TOR), mediates TOR action. Cell 110: 177-189.

Haudek SB, Taffet GE, Schneider MD, Mann DL (2007) TNF provokes cardiomyocyte apoptosis and cardiac remodeling through activation of multiple cell death pathways. Journal Clin Invest 117: 2692-2701.

Hedayat M, Mahmoudi MJ, Rose NR, Rezaei N (2010) Proinflammatory cytokines in heart failure: double-edged swords. Heart Fail Rev 15: 543-562.

Heineke J, Auger-Messier M, Xu J, Oka T, Sargent MA, York A, Klevitsky R, Vaikunth S, Duncan SA, Aronow BJ, Robbins J (2007) Cardiomyocyte GATA4 functions as a stress-responsive regulator of angiogenesis in the murine heart. J Clin Invest 117: 3198-3210.

Heineke J, Molkentin JD (2006) Regulation of cardiac hypertrophy by intracellular signalling pathways. Nature Rev Mol Cell Biol 7: 589-600.

Holz MK, Ballif BA, Gygi SP, Blenis J (2005) mTOR and S6K1 mediate assembly of the translation preinitiation complex through dynamic protein interchange and ordered phosphorylation events. Cell 123: 569-580.

Hotchkiss RS, Strasser A, McDunn JE, Swanson PE (2009) Cell death. New Engl J Med 361: 1570-1583.

Hudlicka O, Brown M, Egginton S (1992) Angiogenesis in skeletal and cardiac muscle. Physiol Rev 72: 369-417.

Hudson CC, Liu M, Chiang GG, Otterness DM, Loomis DC, Kaper F, Giaccia AJ, Abraham RT (2002) Regulation of hypoxia-inducible factor 1α expression and function by the mammalian target of rapamycin. Mol Cell Biol 22: 7004-7014.

Jacinto E, Facchinetti V, Liu D, Soto N, Wei S, Jung SY, Huang Q, Qin J, Su B (2006) SIN1/MIP1 maintains rictor-mTOR complex integrity and regulates Akt phosphorylation and substrate specificity. Cell 127: 125-137.

Janes MR, Limon JJ, So L, Chen J, Lim RJ, Chavez MA, Vu C, Lilly MB, Mallya S, Ong ST, Konopleva M (2010) Effective and selective targeting of leukemia cells using a TORC1/2 kinase inhibitor. Nature Med 16: 205-213.

Kenessey A, Ojamaa K (2006) Thyroid hormone stimulates protein synthesis in the cardiomyocyte by activating the Akt-mTOR and p70S6K pathways. J Biol Chem 281: 20666-20672.

Kostin S, Pool L, Elsässer A, Hein S, Drexler HC, Arnon E, Hayakawa Y, Zimmermann R, Bauer E, Klövekorn WP, Schaper J (2003) Myocytes die by multiple mechanisms in failing human hearts. Circul Res 92: 715-724.

Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP (1990) Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. New Engl J Med 322: 1561-1566.

Lorell BH, Carabello BA (2000) Left ventricular hypertrophy: pathogenesis, detection, and prognosis. Circulation 102: 470-479.

Manning BD, Tee AR, Logsdon MN, Blenis J, Cantley LC (2002) Identification of the tuberous sclerosis complex-2 tumor suppressor gene product tuberin as a target of the phosphoinositide 3-kinase/akt pathway. Mol Cell 10: 151-162.

Matsui T, Rosenzweig A (2005) Convergent signal transduction pathways controlling cardiomyocyte survival and function: the role of PI 3-kinase and Akt. J Mol Cell Cardiol 38: 63-71.

Matsui Y, Takagi H, Qu X, Abdellatif M, Sakoda H, Asano T, Levine B, Sadoshima J (2007) Distinct roles of autophagy in the heart during ischemia and reperfusion: roles of AMP-activated protein kinase and Beclin 1 in mediating autophagy. Circul Res 100: 914-922.

McMullen JR, Sherwood MC, Tarnavski O, Zhang L, Dorfman AL, Shioi T, Izumo S (2004) Inhibition of mTOR signaling with rapamycin regresses established cardiac hypertrophy induced by pressure overload. Circulation 109: 3050-3055.

Mizushima N, Yamamoto A, Matsui M, Yoshimori T, Ohsumi Y (2004) In vivo analysis of autophagy in response to nutrient starvation using transgenic mice expressing a fluorescent autophagosome marker. Mol Biol Cell 15: 1101-1111.

Myers MP, Pass I, Batty IH, Van der Kaay J, Stolarov JP, Hemmings BA, Wigler MH, Downes CP, Tonks NK (1998) The lipid phosphatase activity of PTEN is critical for its tumor supressor function. Proc Nat Acad Sci 95: 13513-13518.

Nakatogawa H, Ichimura Y, Ohsumi Y (2007) Atg8, a ubiquitin-like protein required for autophagosome formation, mediates membrane tethering and hemifusion. Cell 130: 165-178.

Nishida K, Kyoi S, Yamaguchi O, Sadoshima J, Otsu K (2009) The role of autophagy in the heart. Cell Death Differ 16: 31-38.

Olivetti G, Abbi R, Quaini F, Kajstura J, Cheng W, Nitahara JA, Quaini E, Di Loreto C, Beltrami CA, Krajewski S, Reed JC (1997) Apoptosis in the failing human heart. New Engl J Med 336: 1131-1141.

Oudit GY, Kassiri Z, Zhou J, Liu QC, Liu PP, Backx PH, Dawood F, Crackower MA, Scholey JW, Penninger JM (2008) Loss of PTEN attenuates the development of pathological hypertrophy and heart failure in response to biomechanical stress. Cardiovasc Res 78: 505-514.

Pulido R (2018) PTEN Inhibition in human disease therapy. Molecules 23: 285.

Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, Jacobsen SJ (2004) Trends in heart failure incidence and survival in a community-based population. JAMA 292: 344-350.

Sancak Y, Bar-Peled L, Zoncu R, Markhard AL, Nada S, Sabatini DM (2010) Ragulator-Rag complex targets mTORC1 to the lysosomal surface and is necessary for its activation by amino acids. Cell 141: 290-303.

Sancak Y, Peterson TR, Shaul YD, Lindquist RA, Thoreen CC, Bar-Peled L, Sabatini DM (2008) The Rag GTPases bind raptor and mediate amino acid signaling to mTORC1. Science 320: 1496-1501.

Sano M, Minamino T, Toko H, Miyauchi H, Orimo M, Qin Y, Akazawa H, Tateno K, Kayama Y, Harada M, Shimizu I (2007) p53-induced inhibition of Hif-1 causes cardiac dysfunction during pressure overload. Nature 446: 444-448.

Scheuer J, Malhotra A, Hirsch C, Capasso J, Schaible TF (1982) Physiologic cardiac hypertrophy corrects contractile protein abnormalities associated with pathologic hypertrophy in rats. J Clin Invest 70: 1300-1305.

Sharma HS, Stahl J, Weisensee D, Löw-Friedrich I (1996) Cytoprotective mechanisms in cultured cardiomyocytes. In: Krause EG, Vetter R (eds.): Biochemical Mechanisms in Heart Function, Springer, Boston, MA, pp. 217-224.

Shioi T, Matsumori A, Kihara Y, Inoko M, Ono K, Iwanaga Y, Yamada T, Iwasaki A, Matsushima K, Sasayama S (1997) Increased expression of interleukin-1β and monocyte chemotactic and activating factor/monocyte chemoattractant protein-1 in the hypertrophied and failing heart with pressure overload. Circul Res 81: 664-671.

Shioi T, McMullen JR, Tarnavski O, Converso K, Sherwood MC, Manning WJ, Izumo S (2003) Rapamycin attenuates load-induced cardiac hypertrophy in mice. Circulation 107: 1664-1670.

Shiojima I, Sato K, Izumiya Y, Schiekofer S, Ito M, Liao R, Colucci WS, Walsh K (2005) Disruption of coordinated cardiac hypertrophy and angiogenesis contributes to the transition to heart failure. J Clin Invest 115: 2108-2118.

Shiojima I, Walsh K (2006) Regulation of cardiac growth and coronary angiogenesis by the Akt/PKB signaling pathway. Genes Devel 20: 3347-3365.

Siwik DA, Chang DL, Colucci WS, (2000) Interleukin-1beta and tumour necrosis factor-alpha decrease collagen synthesis and increase matrix metalloproteinase activity in cardiac fibroblasts in vitro. Circ Res 86: 1259–1265.

Stephens L, Anderson K, Stokoe D, Erdjument-Bromage H, Painter GF, Holmes AB, Gaffney PR, Reese CB, McCormick F, Tempst P, Coadwell J (1998) Protein kinase B kinases that mediate phosphatidylinositol 3, 4, 5-trisphosphate-dependent activation of protein kinase B. Science 279: 710-714.

Sui L, Wang J, Li BM (2008) Administration of triiodo-L-thyronine into dorsal hippocampus alters phosphorylation of Akt, mammalian target of rapamycin, p70S6 kinase and 4E-BP1 in rats. Neurochem Res 33: 1065-1076.

Sun M, Chen M, Dawood F, Zurawska U, Li JY, Parker T, Kassiri z, Kirshenbaum LA, Arnold M, Khokha R, Liu PP (2007) Tumour necrosis factor-alpha mediates cardiac remodelling and ventricular dysfunction after pressure overload state. Circulation 155: 1398–1407.

Takimoto E, Champion HC, Li M, Ren S, Rodriguez ER, Tavazzi B, Lazzarino G, Paolocci N, Gabrielson KL, Wang Y, Kass DA (2005) Oxidant stress from nitric oxide synthase–3 uncoupling stimulates cardiac pathologic remodeling from chronic pressure load. J Clin Invest 115: 1221-1231.

Tirziu D, Chorianopoulos E, Moodie KL, Palac RT, Zhuang ZW, Tjwa M, Roncal C, Eriksson U, Fu Q, Elfenbein A, Hall AE (2007) Myocardial hypertrophy in the absence of external stimuli is induced by angiogenesis in mice. J Clin Invest 117: 3188-3197.

Toker A, Cantley LC (1997) Signalling through the lipid products of phosphoinositide-3-OH kinase. Nature 387: 673-676.

Vanhaesebroeck B, Guillermet-Guibert J, Graupera M, Bilanges B (2010) The emerging mechanisms of isoform-specific PI3K signalling. Nature Rev Mol Cell Biol 11: 329-341.

Weichhart T, Säemann MD (2009) The multiple facets of mTOR in immunity. Trends Immunol 30: 218-226.

Wencker D, Chandra M, Nguyen K, Miao W, Garantziotis S, Factor SM, Shirani J, Armstrong RC, Kitsis RN (2003) A mechanistic role for cardiac myocyte apoptosis in heart failure. J Clinical Invest 111: 1497-1504.

Whelan RS, Kaplinskiy V, Kitsis RN (2010) Cell death in the pathogenesis of heart disease: mechanisms and significance. Ann Rev Physiol 72: 19-44.

Wick M (1999) Filament assembly properties of the sarcomeric myosin heavy chain. Poultry Sci 78: 735-742.

Wong GHW, Goeddel DV (1988) Induction of manganous superoxide dismutase by tumor necrosis factor: possible protective mechanism. Science 242: 941-944.

Yamauchi-Takihara K, Kishimoto T (2000) Cytokines and their receptors in cardiovascular diseases—role of gp130 signaling pathway in cardiac myocyte growth and maintenance. Int J Exp Pathol 81: 1-16.

Yang Q, Guan KL (2007) Expanding mTOR signalling. Cell Res 17: 666–681.

Yu X, Kennedy RH, Liu SJ (2003) JAK2/STAT3, not ERK1/2, mediates interleukin-6-induced activation of inducible nitric-oxide synthase and decrease in contractility of adult ventricular myocytes. J Biol Chem 278: 16304-16309.

Zak R, Rabinowitz M (1979) Molecular aspects of cardiac hypertrophy. Ann Rev Physiol 41: 539-552.

Zhang P, Xu X, Hu X, Van Deel ED, Zhu G, Chen Y (2007) Inducible nitric oxide synthase deficiency protects the heart from systolic overload–induced ventricular hypertrophy and congestive heart failure. Circ Res 100: 1089-1098.

Zhang S, Cui R (2018) The targeted regulation of miR-26a on PTEN-PI3K/AKT signaling pathway in myocardial fibrosis after myocardial infarction. Eur Rev Med Pharmacol Sci 22: 523-531.

Zhong H, Chiles K, Feldser D, Laughner E, Hanrahan C, Georgescu MM, Simons JW, Semenza, GL (2000) Modulation of hypoxia-inducible factor 1α expression by the epidermal growth factor/phosphatidylinositol 3-kinase/PTEN/AKT/FRAP pathway in human prostate cancer cells: implications for tumor angiogenesis and therapeutics. Cancer Res 60: 1541-1545.