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

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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 Molkenin 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 Molkenin 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 (PDK1) 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/

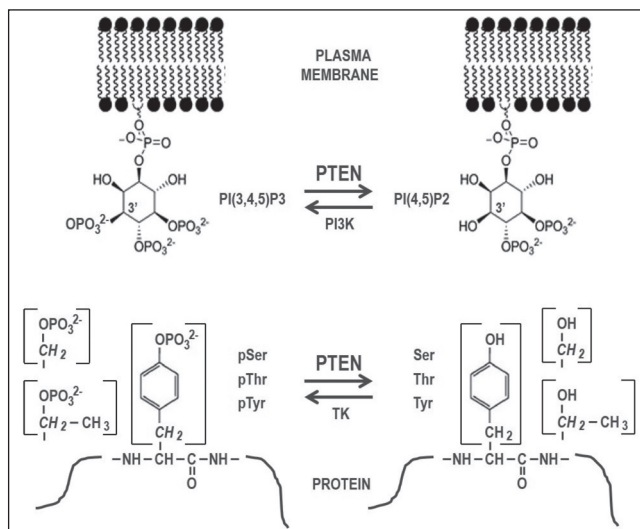


Fig. 1: Schematic representation of PTEN dephosphorylation and reverse catalytic reaction (Pulido 2018).

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; Coffey 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; Coffey 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 (Coffey 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 (Coffey and Woodgett 1998). The tumour suppressor and the peroxisome proliferator-stimulated  $\gamma$ -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; Coffey 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) (Coffey 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 (Coffey 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 p85 $\alpha$  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 prudent 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 biome-

chanical 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).

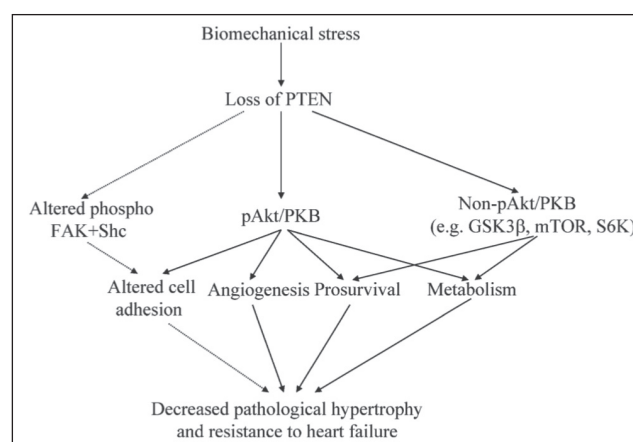


Fig. 2: Representation of the functions of PTEN in the myocardial reaction to maladaptive biomechanical stresses (Oudit et al. 2008).

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-26a are upregulated after infarction in the myocardium (Sharma et al. 1996). Depending on the extent of myocardial fibrosis, miR-26a 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; Siwik et al. 2000). Furthermore, it dephosphorylates PI3P to antagonise its phosphorylation effects on PI2P, hence inhibiting downstream and Akt signalling pathway stimulation (Yamauchi-Takahara 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 metalloproteinase 9 (MMP-9) (Yu et al. 2003).

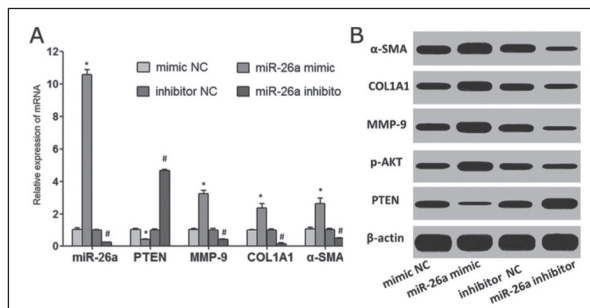


Fig. 3. MMP-9 and miR-26a modulated Akt/PI3K activity expression in hypertrophic cardiac tissues (Zhang and Cui 2018). A shows mRNA expressions detected by qRT-PCR. B is the protein expressions identified by Western blot method (Zhang and Cui 2018; Aukrust et al. 2005).

## 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 hamartomas 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.

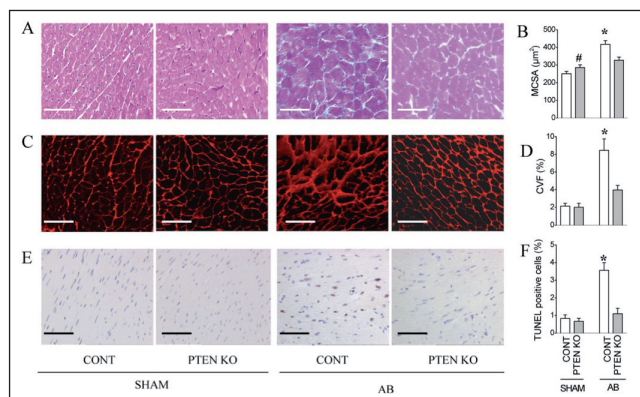


Fig. 4. Reduced interstitial fibrosis, apoptosis, and cardiac hypertrophy in PTEN KO mouse in reaction to eight weeks of overload in pressure (Oudit et al. 2008). A denotes trichrome parts; B represents the cardiomyocyte cross-sectional area (MCSA); C shows Picrosirius red sections using a confocal microscope; 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.

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