Review Article

Cardiac Hypertrophy: A Review on Pathogenesis and Treatment

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ABSTRACT
Cardiac hypertrophy has been considered as an important risk factor for cardiac morbidity and mortality whose prevalence has increased during the last few decades. Cardiac hypertrophy, a disease associated with the myocardium, is characterized by thickening of ventricle wall of heart and consequent reduction in the contracting ability of heart to pump the blood. Cardiac hypertrophy has been divided into two types, i.e. physiological and pathological hypertrophy. The exercise-induced increase in the ability of pumping blood leads to thickening of ventricle wall, referred to as physiological hypertrophy. On the other hand, reduced ability of pumping blood as a result of hypertension and volume overload on heart denotes pathological hypertrophy. Numerous mediators have been found to be involved in the pathogenesis of cardiac hypertrophy that include mitogen-activated protein kinase (MAPK), protein kinase C (PKC) insulin-like growth factor-I (IGF-I), phosphatidylinositol 3-kinase (PI3K)-AKT/PKB, calcinurin-nuclear factor of activated T cells (NFAT) and mammalian target of rapamycin (mTOR). The prevention strategy for cardiac hypertrophy involve thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin (Ang) II receptor blockers, beta blockers and calcium channel blockers. The present review article highlights the signaling mechanisms involved and the approaches required in the treatment of cardiac hypertrophy.

Keywords: Cardiac hypertrophy, Ventricle, Physiological, Pathological.

INTRODUCTION

It has been known since 1990s that biochemical signaling events and changes in gene expression are important for hypertrophic response. [1-3] Such phenomenon lead to the protein synthesis and increase in cell size, which are the characteristics features of hypertrophic pattern. [4] Cardiac hypertrophy is a disease associated with the heart in which the ventricle wall of heart get thickened, mainly left ventricle, which is more susceptible to hypertrophy. In this disease, the ability of pumping the blood gets decreased that ultimately results in cardiac dysfunction. [5-6] Cardiac hypertrophy is regarded as the myocardial response to a variety of extrinsic and intrinsic stimuli that impose increased biomechanical stress. The diagnosis is usually based on the calculated echocardiographic or magnetic resonance imaging estimate of the left ventricular mass. Further, the cardiac hypertrophy may be classified as physiological and pathological hypertrophy. [7-8] Cardiac hypertrophy may develop due to pressure and volume over load on the

myocardium. Other possible causes include high blood pressure, heart valve disease, weakness of heart muscle, abnormal heart beat, anemia, thyroid disorders, excessive iron in the body, protein build up in the heart and amyloidosis, which collectively have been noted to reduce adenosine triphosphate (ATP) synthesis in cardiac mitochondria ultimately leading to the development and progression of cardiac hypertrophy. [9] Various signaling mechanisms have been found to be implicated in the pathogenesis of cardiac hypertrophy that includes MAPK, PKC, NFAT, PI3K-AKT/PKB, M-TOR and IGF-1. [9-13] Moreover, the treatment strategies of cardiac hypertrophy include calcium channel blockers, beta blockers, thiazide diuretics, angiotensin converting enzyme (ACE) inhibitors and Ang-II receptor blockers. [14-16] The present review explains about various signaling mechanisms involved in the development and progression of cardiac hypertrophy. Moreover, treatment strategies for cardiac hypertrophy have also been delineated in the present review.

Classification of Cardiac Hypertrophy

Cardiac hypertrophy has been classified as physiological and pathological hypertrophy which can be sub-classified as concentric or eccentric based on changes in shape that are dependent on the initiating stimulus. [17-18] Physiological

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hypertrophy is the normal response to healthy exercise or training, which results in increased myocardial muscle mass and pumping ability. [19] The pathological hypertrophy is the response of myocardium to any disease such as hypertension, myocardial infarction, valvular heart disease and genetic mutations. The pathological hypertrophy leads to an increased muscle mass and accumulation of collagen inside the myocardium. [20-21] A pathological stimulus causing pressure overload produces an increase in systolic wall stress that results in concentric hypertrophy which is characterized by thick walls and relatively small cavities in the myocardium, whereas, a pathological stimulus causing volume overload produces an increase in diastolic wall stress resulting in eccentric hypertrophy which is characterized by large dilated cavities and relatively thin walls in the myocardium. [8, 17-18] Isotonic exercise like running, walking, cycling and swimming involve movement of large muscle groups. The intense vasodilatation of the skeletal muscle vasculature produces eccentric hypertrophy by increasing the venous return to the myocardium causing volume overload, characterized by chamber enlargement and a proportional change in wall thickness. [18, 22]
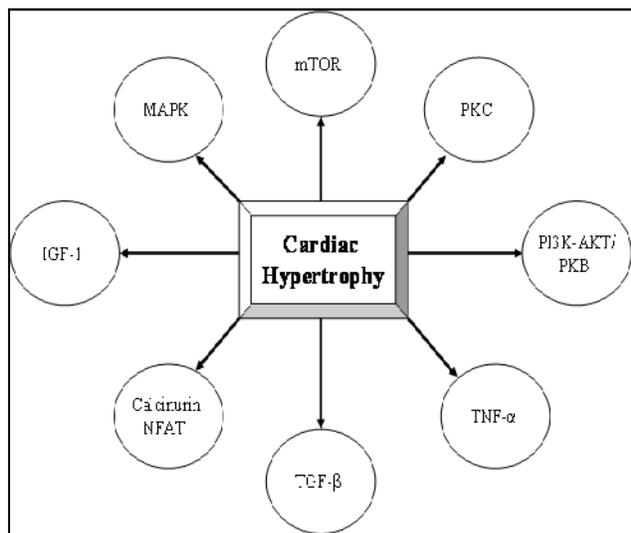

Fig. 1: Diagram showing signaling pathways of Cardiac Hypertrophy
MAPK-mitogen-activated protein kinase; PKC-Protein kinase C; IGF-1-Insulin-like growth factor-I; (PI3K)-AKT/PKB phosphatidylinositol 3-kinase-Akt/Protein Kinase B; Calcineurin NFAT-nuclear factor of activated T cells; mTOR-mammalian target of rapamycin; TNF-α-tumor necrotic factor-alpha; TGF-β-Transforming growth factor-beta

The isometric exercise like weight lifting involves muscular tension development against resistance and the mechanical changes produces pressure load on the heart resulting in concentric hypertrophy. In pathological hypertrophy, the enlargement of cardiac myocytes along with formation of new sarcomeres normalizes ventricle wall stress and allows normal cardiovascular function at rest, known as compensated growth. [23-24] Moreover, function in the hypertrophied heart eventually decompensate ultimately leading to left ventricle dilation and heart failure whereas, physiological hypertrophy does not decompensate into dilated cardiomyopathy or heart failure. [8, 18, 22, 25]

Signaling Mechanisms involved in Cardiac Hypertrophy
Various signaling mechanisms are involved in the development of cardiac hypertrophy that includes MAPK;

PKC; Calcinurin NFAT System; IGF-1; PI3K-AKT/PKB; m-TOR; tumor necrotic factor-alpha (TNF-α); transforming growth factor-beta (TGF-β) (Fig. 1). It has been reported that MAPK plays a very important role in the induction of cardiac hypertrophy. [26-27] The MAPK signaling pathway consists of three major phosphorylation spill that include ERK (Extra cellular signal regulated protein kinase), the c-Jun NH$_2$-terminal kinase (JNK) and p38 MAP kinase. JNK and p38 are mainly activated by stress type stimuli. [28-29] There is the activation of the MKK6 and MKK3 that gives rise to the signals of hypertrophy. [30] JNK is also activated by the pressure overload and Ras that also induce hypertrophic response by the activation of the adrenergic system. [31] Thus it can be reported that JNK and p38 play a vital role in the induction of the cardiac hypertrophy. [30] It has been shown that calcinurin-NFAT and MAPK are co-dependent that may cause activation of the calcinurin in myocyte leading to up-regulation in ERK and JNK along with down regulation of the p38 signaling. Simultaneously, the unitary action of the JNK and p38 from the MAPK in cardiac myocyte leads to down regulation of the calcinurin effectiveness by direct antagonistic effect of the nuclear factor of activated T-cells. [12, 27] Thus it can be suggested that the Calcinurin-NFAT is one of the responsible factor for the hypertrophic response in the heart.

It has been discussed earlier that multiple signals are present which may responsible for the induction of cardiac hypertrophy. PKC is a ubiquitously expressed serine/ threonine kinase that is activated by Gq/G11-coupled receptors. Multiple studies implicate the various PKC isoforms in the pathogenesis of cardiac hypertrophy. Interestingly, it has been noted that calcineurin plays an important role in the activation of PKC. PKC isoforms are activated in the heart following agonist induced G-protein coupled receptors. [32] Mechanical stretch of the left ventricle induces translocation of PKC-epsilon whereas chronic pressure overload activates PKC-α. Once PKC is activated by calcineurin, the hypertrophic gene expression gets directly enhanced leading to the development and progression of cardiac hypertrophy. [33] IGF-1 induces cardiac hypertrophy by causing alteration in the potassium channels responsible for the generation of action potential repolarization. This process mainly acts through MAPK and PI3K pathways. [34] The potassium channels are positively maintained by steady state Akt and ERK activities. K$^+$ channels seem to be regulated in dichotomic manner by acutely stimulated MAPKs and Akt. Thus activation of IGF-1 via MAPKs and PI3K are responsible for the induction of cardiac hypertrophy. [35-36] IGF-I have been suggested to regulate developmental and physiological growth of the heart. Ligand binding to the IGF-I receptor has been noted to activate PI3K of the IA group, PI3Kα, a heterodimer that consists of a p85 regulatory sub unit and a p110 (α, β or δ) catalytic subunit. [37] Further, PI3K converts the plasma membrane lipid phosphatidylinositol-4, 5-bisphosphate (PIP$_2$) to phosphatidylinositol-3, 4, 5-tri phosphate (PIP$_3$), which activates other signaling constituents at the plasma membrane. [37-38] Moreover, PI3K activation results in the sarcolemmal recruitment of the kinases AKT/PKB through its pleckstrin-homology domains. It has been demonstrated that PI3K-AKT/PKB signalling is important for the physiological growth of the heart that evidenced the role of PI3K-AKT/PKB in cardiac hypertrophy. [13, 39] In addition,

activated PI3K-AKT/PKB induces cardiac hypertrophy that is associated with preserved function, i.e., compensated hypertrophy. Conversely, the constitutive over expression of PI3K-AKT/PKB leads to cardiac dysfunction which was evidenced over the time in some models. [12, 40-41].

Other signaling mechanism that has been reported to be involved in the activation of cardiac hypertrophy is m-TOR. [40] The m-TOR is activated by ERK signaling and PI3K, which stimulate protein synthesis. Moreover, ERK signaling plays an important role in the development of the cardiac hypertrophy as it is one of the signaling components of the MAPK. Moreover, the regulatory role of m-TOR in the development and progression of cardiac hypertrophy has been evidenced by the fact that the inhibition of mTOR significantly treated pathological hypertrophy. [11, 42] It has previously been shown that the signaling mechanisms are interrelated to each other. TGF-β enhances the risk of cardiac hypertrophy by PKC-induced activation, which leads to the increased myocyte protein content, cell size and sarcomeric organization. [43]. It has also been reported that TNF-α is involved in the production of pathological condition indicated by cardiac hypertrophy. It has been suggested that TNF-α increases oxidative stress in the myocardial cells by changing the mitochondrial redox state and membrane permeability transition pore opening, which ultimately leads to cardiac hypertrophy. [12, 44] G-protein coupled receptors (GPCRs) play an important role in the regulation of cardiac function and adaptation to changes in hemodynamic burden. GPCRs have been found to act by three pathways, firstly, they bind with β-adrenergic system leading to the increase in heart rate in response to the epinephrine; secondly, they bind with acetylcholine that further leads to an increase in the contractility of the heart; and thirdly, it binds with the Ang II, endothelin and α-adrenergic receptors. These pathways collectively interfere with the normal functioning of the heart that further lead to excessive load on the heart ultimately resulting in the development and progression of cardiac hypertrophy. [45-47]

Treatment of Cardiac Hypertrophy
The treatment strategies of cardiac hypertrophy include exercise, monitoring blood pressure and use of antihypertensive drugs. Various class of drugs have been suggested to have a modulatory role in the treatment of cardiac hypertrophy that include thiazide diuretics like chlorthiazide, hydrochlorothiazide; ACE inhibitors like enalapril, lisinopril and captopril; Ang-II receptor blockers like Losartan, Azilsartan; β-blockers like atenolol, carvedilol, metoprolol, bisoprolol; Calcium channel blockers like amlodipine, diltiazem, nifedipine, and verapamil. [14-16, 48] Another strategy that has been reported for the treatment of cardiac hypertrophy is surgical treatment which can be performed by septal myectomy and septal ablation. [49] Septal myectomy is considered as surgical treatment for cardiac hypertrophy that involves removing of a portion of the septum which was obstructing the stream of blood from the left ventricle to the aorta. [50-51] Septal myectomy is performed to reduce the muscle thickening that occurs in patients with hypertrophic cardiomyopathy (HCM). Septal myectomy has been regarded as one of the prominent treatment options for HCM patients when symptoms persist regardless of the optimal treatment with drug medications. [52-53]

Another technique of surgical procedure is alcohol septal ablation (ASA, TASH, Sigwart procedure) which is a percutaneous, minimally-invasive treatment performed by a cardiologist to relieve symptoms and improve functional status in HCM symptomatic patients with strict clinical, anatomic and physiologic selection criteria. Special attention should be given towards the selection of the patient when performed by an experienced interventional cardiologist. [54] ASA is a technique which reduces the obstruction to the blood being ejected from the heart. The technique creates a small controlled heart attack during which the area of cardiac muscle responsible for the obstruction is killed that ultimately makes the obstructed area thin. [55] The technique is similar to coronary angioplasty and utilizes similar equipments including the utilization of wires and balloons to localize the septal artery feeding the diseased cardiac muscle. [56-57]

Cardiac hypertrophy represents one of the important cardiovascular problems all over the world today. We have presented some well defined pathways that modulate the development and progression of cardiac hypertrophy. A significant future challenge in the field is to translate the knowledge of these signaling mechanisms into novel pharmacological and gene therapeutic treatments for pathological cardiac hypertrophy and cardiac failure. The generation of novel selective inhibitors with low toxicity could provide new opportunities for alleviating the deadly heart disease. Hence, new studies are warranted in order to provide potential drug therapies that could certainly alleviate cardiac hypertrophy in order to prolong the quality of life at the ground level.

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