Analyzing and Identifying the Molecular Targets and Regulators Controlling Cardiac Hypertrophy Progression

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ABSTRACT

Cardiac hypertrophy is the major pathway by which neurohormonal and mechanical stimuli act upon cardiomyocytes which gives the response to these stimuli. It leads to heart failure and ventricular dilation which is the main root of mortality in the western world. Many molecular targets are controlling cardiac hypertrophy development which may influence the growth factors signaling, cytokine release and gene expression. Through clinical trials on different models, recent research shows that cardiac hypertrophy might be inhibited or reversed. These findings have developed a vast drive to recognize specific and novel regulators of cardiac hypertrophy. Many molecular targets and signaling modulators have been studied in this review that induce the hypertrophic response which may involve MAPK pathway, oxidative stress, calcineurin, Cardiac angiogenesis, serum protein concentration, microRNA, and periodontitis. For the treatment of cardiac hypertrophy, the scientific knowledge of these signaling pathways and factors may be translated into potential nutritional and molecular therapies for the betterment of this diseases. The current and previous knowledge of molecular markers can be compiled in this review for the treatment of the molecular pathogenesis of cardiac hypertrophy.

Keywords: Cardiac hypertrophy, miRNA, Angiogenesis, Oxidative stress

INTRODUCTION

Diseases of cardiac remain the prime root of death in the world, with congestive heart failure that illustrates the major cause and rapidly growing subclass over the past decade (Ali, El-Dahshan, & Yahia, 2017). Cardiac hypertrophy is the result of an increase in biomechanical stress on the cell in which the heart undergoes abnormal enlargement, or thickening of the cardiac muscles, as a result increases cardiomyocyte size and changes in other heart muscle components, like the extracellular matrix (DeFrancesco, 2021). Different molecular mechanisms are reported to be involved in the development of cardiac hypertrophy. Many external stimuli and molecular mechanisms categorized cardiac hypertrophy into two types, physiological hypertrophy, mainly in the Athlete's heart, characterized by enhanced contractile function and pathological hypertrophy occurred by hypertension (Mehdiyev, Mustafaev, & Mamedov, 2021). Structural heart diseases or myocardial Infarction is linked with the re-expression of fetal cardiac genes such as genes that code for β-myosin chain and natriuretic peptides (Dukkipati et al., 2017). Many genes other than fetal genes have been identified by the expression analysis on a large-scale which were involved in the upregulation of hypertrophied heart as well as involved in signaling pathways and energy metabolism by the expression of gene encoding protein (Akasia & Komura, 2003).

Hypertrophic stimulation is responsible for the different gene expression. Cardiac transcription factors directly regulate many cardiac genes and play a leading vital role in the upregulation of hypertrophied myocardium (Churko et al., 2018). Gupta identifies oxidative stress as one of the major factors involved in cardiac hypertrophy development (Gupta, Das, & Sen, 2007).

Clinical studies on neonatal cultured cardiomyocytes and transgenic mice show that overexpression of GATA-4 is sufficient for inducing hypertrophy and cardiac angiogenesis (Malek Mohammadi et al., 2017). MicroRNAs have been connected in myocardial disease processes (Kura et al., 2019). Experiments on cultured cardio myocytes identified that the upregulation of many miRNAs in heart failure induced molecular changes that are like seen in cardiac hypertrophy (Kura et al., 2019). Some miRNAs are reported to be downregulated and some are upregulated thus, indicating their role in hypertrophic response (Szczerba et al., 2020).

Other factors like inhibition of FPPS diminished angiotensin II which initiates cardiac hypertrophy and fibrosis by decreasing Rhoda activity (Dai et al., 2017). The concentrations of vitamin D, intact parathyroid hormone, and Fetuin-A in serum were seen to be closely linked with cardiac hypertrophy (Nizameddin et al., 2019). Although a great relationship between periodontitis and cardiovascular disease has been studied, through which it is announced that myocardial hypertrophy might be afflicted by periodontitis (Sato et al., 2017; Seminice et al., 2012). Further In this review we will discuss details that how different molecular mechanisms and factors regulate cardiac hypertrophy and about therapeutic targets in the future that many novel therapeutic drugs and mechanisms are predicted by characterized signaling circuits for heart diseases treatment.

MOLECULAR PATHWAYS AND TARGETS THAT CONTROLLING CARDIAC HYPERTROPHY

Different factors, pathways and regulators have been shown to involve in the regulation

of cardiac hypertrophy and its progression including oxidative stress, the impact of miRNAs, Angiogenesis and different pathogenic diseases associate with cardiac hypertrophy (Figure 1).

Figure 1: Overview of all Molecular Targets and their Controlling Mechanisms
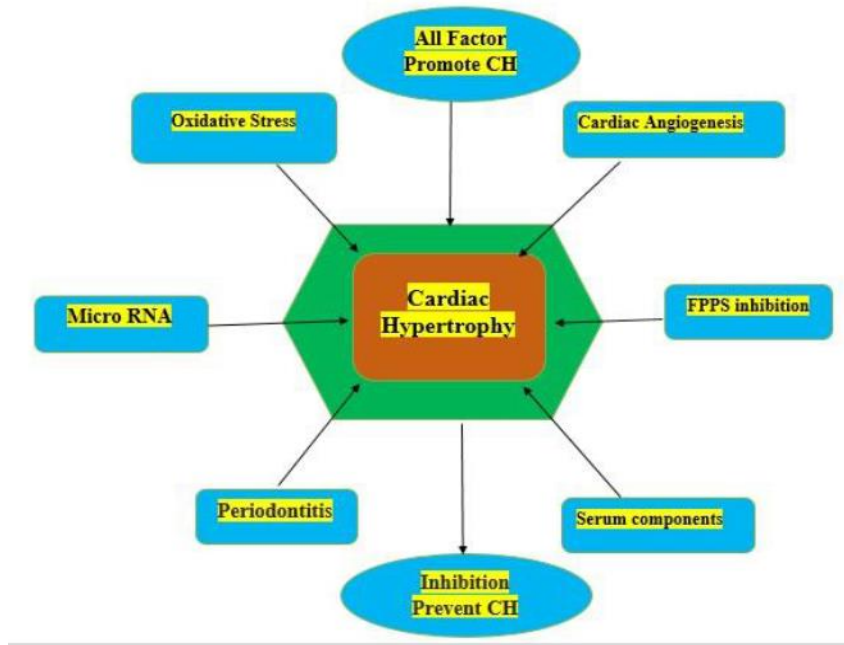
Oxidative Stress

Oxidative stress hurts cardiac structure and function is unclear but various studies revealed that redox-sensitive signaling pathways have a causative role in the development of cardiac hypertrophy (Faria & Persaud, 2017). The increasing level of oxidative stress have a harmful damaging effect on DNA and membrane as well as the enzymes associated with cellular homeostasis (Haque, Nam, Eom, Kim, & Rhee, 2020). In a biological system, the double role of reactive oxygen species is either beneficial or harmful to living entities. Unregulated excessive ROS is cytotoxic, causing damage to cellular macromolecules and are involved in several pathological conditions (Cheng et al., 2021). Defective mitochondrial electron transport chain, dysfunctional nitric oxide synthase, xanthine oxidase and NADPH are the major sources to produce ROS which is responsible for the induction of cardiac hypertrophy (Zhang, Murugesan, Huang, & Cai, 2020). In cardiovascular cells ROS is continuously produced by NADPH oxidase. Angiotensin II, TNF-α, cyclic stretch and endothelin-1 are the different stimuli that enhanced the activity of ROS (Pena, Brito, El Alam, & Siques, 2020). Insulin-induced ROS generation in an NADPH oxidase-dependent manner, additionally stimulates PI3K and PKC signaling (Biswas, Mukherjee, Tarsal, Singh, & Mukhopadhyay, 2013). Mitochondrial dysfunction and xanthine

oxidase are also found to be responsible for CH development.

Many important signaling pathways are modulated by ROS in stretched-induced cardiomyocyte hypertrophy. Serine/ threonine kinases receptor, tyrosine kinases receptor, cardiotrophin-1 receptors are the receptor on cardiac myocytes that is initiated by MAPK signaling cascade (Yongtao Zhang et al., 2020). ROS are important for stretch-induced activation of p38MAPK (J. Liu et al., 2021). Many transcription factors and multiple intracellular targets are phosphorylated by activated p38, JNKs and ERKs have been reported to involve in the remolding of cardiac gene expression.

CARDIAC ANGIOGENESIS

Coronary angiogenesis is impaired in the chronic phase which enhanced in the acute phase. Contractile dysfunction and impaired cardiac growth are caused by the inhibition of angiogenesis in the early phase (S. Liu et al., 2020). Enhanced coronary angiogenesis is associated with physiological cardiac growth having contractile function but impaired coronary angiogenesis is associated with pathological cardiac hypertrophy by reducing contractile function (T. Liu et al., 2020). Precursor cells of angiogenic, angioblasts from the sinus venosus and the proepicardial organ can separate into endothelial cells and assemble in a crude narrow organization in an interaction called coronary vasculogenic. Angiogenesis as well as physiological neovascularization expands the myocardial vascular plexus after birth, in which endothelial progenitor cells are involved (Luton & Carmelite, 2004; Riley, 2012). During the physiological growth phase, the inhibition of coronary angiogenesis is responsible for contractile dysfunction,

impaired cardiac growth, and pathological hypertrophy. As the result of pathological hypertrophy capillary density was reduced and in the case of physiological cardiac hypertrophy a significant increase in the number of myocardial capillaries was observed (Oldfield, Duhamel, & Dhalla, 2020). Fibroblast growth factors, angiogenic growth factors, transforming growth factors VEGF sangiopoirtin-1 and -2 and platelet-derived growth factors regulated the myocardial angiogenesis. This study suggested that cardiomyocytes themselves produce angiogenic factors to maintain capillary density, oxygen supply, and function. To enhance myocardial angiogenesis have been investigated due to several strategies including growth factors delivery of angiogenic genes. The angiogenic factors include VEGF-A, VEGFB, stromal cell-derived factor-1, midline, VEGF-B, fibroblast growth factor-5, hepatocyte growth factor, and fibroblast growth factor 2. Immature angiogenesis and increase in vascular permeability occurred due to long-term stimulation with VEGF-A Similarly stimulation with angiopoietin-1 and VEGF-A (Eguchi & Wakabayashi, 2020) are involved in improved cardiac perfusion and porcine models of MI-A combined effect of hepatocyte growth factor and fibroblast growth factor-2 stimulated angiogenesis and prevented the progression of heart failure.

MICRO RNA (MIRNA)

A class of non-coding and single-stranded RNA that is made up of roughly 22 nucleotides in length is commonly known as microRNA (Anusree, Navis, & Prasobh, 2020). About 500 miRNAs are cloned and sequenced in humans, and about 1000 miRNA genes are estimated in the human genome (Anusree et al., 2020). Various

pathological and biological processes are directly regulated by miRNA. Increasing evidence shows the involvement of miRNAs in cardiomyopathies (Fulgencio-Covián et al., 2020). miRNA upregulated the CH development by the overexpression of some miRNA whereas some downregulated the cardiomyocyte hypertrophy by the overexpression of miRNA. Mir-199b and miR-133, belonging to the same transcriptional units are reported to be downregulated in inducing cardiac hypertrophy asdemonstrated in mouse and human models (Jiang et al., 2019). The cardiac hypertrophy can be prevented by the overexpression of miR-99b and Mir-133 in vitro whereas in the cell the inhibition of miR-133 by infusion of antimine antisense oligonucleotide cause marked the development of CH. These are due to different regulatory targets that are regulating hypertrophy like Rhoda and cdc-42. However, the overexpression of miRNA-133b reduced the expression of the hypertrophy gene in the cell whereas the downregulation of miRNA-133b induces the expression of the hypertrophy gene (Y. Liu, Liang, Zhang, & Fu, 2017).

Overexpression of miRNA-199b in human and mouse leads to heart failure by targeting to NFAT or Calcineurin pathway. miRNA-199b direct targets to dual-specificity like tyrosine phosphorylation nuclear NFAT kinase that affect calcineurin-responsive gene expression by increasing Dyrk1a gene expression However, miRNA-199b can be inhibited by a specific antagomir that reduced nuclear NFAT activity by maintaining Dyrk1a expression in the cell which may leads to the reversion of cardiac hypertrophy in the heart failure mouse model (Duygu et al., 2017). These studies show that miRNAs play an essential role in disease formation such as, potential targets of novel therapies (Duygu et al., 2017).

FPPS INHIBITION

Farnesyl pyrophosphate synthase (FPPS) has an assumed part in the pathway of mevalonate. Farnesyl pyrophosphate synthase is a fundamental catalyst for the formation of geranyl pyrophosphate and farnesyl pyrophosphate (Waller, Park, & Tsantrizos, 2019). However, FPP is likewise responsible for the formylation of little GTPases such as Ras; known to be a signal transducer. Heart repairing in the cardio myocytes is solidly connected with the hyperactivity of Ras (Ramos-Kuri et al., 2015). Prior examinations have noticed that hindrance of FPPS lessened angiotensin II that start heart hypertrophy and fibrosis by diminishing movement of Rhoda (Yang et al., 2013). In any case, FPPS overexpression incited cardiovascular hypertrophy and impairment by expanding the expression of RhoA (Yang et al., 2013). Overproduction of Ras support the increment of RhoA in pressing pressure impact heart hypertrophy (Chen et al., 2013) The concealment of farnesyl transferase may likewise increment heart restoring in promptly hypertension rodents by diminishing the action of RAS.

SERUM COMPOSITION CONCENTRATION

The concentration levels of Fetuin A, Vitamin D, and parathyroid hormone were firmly connected with cardiovascular hypertrophy (Zechner & Towler, 2018). With the way toward maturing the occurrence of sarcopenia happen because of involuntary decrease in free of fat muscle mass and heart hypertrophy increments (Chang et al., 2017) . Albeit heart hypertrophy happens with the way toward aging because of cell loaded up

with fibrotic (Chang et al., 2017). Nonetheless, the balance between hormone parathyroid and Lit.D. Expanded PTH convinces cardiovascular hyper contractility ultimately causes receptive heart hypertrophy. Fetuin-A is an inhibitor of calcification and it is associated with resistance of insulin (Bourebaba & Marycz, 2019). Fet-A is additionally contributed to the improvement of diastolic cardiovascular arrest (Bourebaba & Marycz, 2019).

PERIODONTITIS AND MYOCARDIAL HYPERTROPHY

Although a great correlation between periodontitis and cardiovascular disease has been studied, through which it is announced that myocardial hypertrophy might be afflicted by periodontitis (Suzuki et al., 2017). However, the clinical information has some sort of study constraint they firmly propose direct cooperation between left ventricular hypertrophy & harshness of periodontitis. The comprehensive mechanisms between periodontitis and myocardial hypertrophy have not been well understood (Suzuki et al., 2017). However, the periodontal bacterial infection is firmly relevant to myocardial hypertrophy. The periodontal pathogen, Aggregatibacter actinomycetemcomitans has been shown to increase cardiac hypertrophy in murine transverse aortic constriction model, with matrix metalloproteinase-2 activation, however another pathogen Porphyromonas gingivalis (P.g.) did not enhance these pathological changes. In the treatment of slow heartbeat like isoproterenol-induced myocardial hypertrophy model and prohormones gingival is induced myocardial hypertrophy with the help of Toll-like receptor-2 signaling. As our study reported that the periodontitis has a major role in the modulation of chronic inflammation, so it also might have a play role in the medication of myocardial hypertrophy. Table 1: Comparison of molecular targets and controlling mechanism of Cardiac Hypertrophy

CONCLUSION

Table: -1 Comparison of molecular targets and controlling mechanism of Cardiac Hypertrophy

Molecular Targets		Expression	Cardiac Hypertrophy	Controlling Mechanism
Oxidative stress		Increasing	Promote CH	Imbibition
Cardiac Angiogenesis		High Production	Promote CH	Inhibition
Micro RNA	mRNA-199b	Upregulated	Promote CH	Inhibition
	mRNA-133b	Downregulated	Promote CH	Overexpression
FPPS inhibition		Overexpression	Promote CH	Inhibition
Serum components	Vitamin D	High Concentration	Promote CH	Balance Concentration
	Parathyroid hormone	High Concentration	Promote CH	
	Fetuin A	High Concentration	Promote CH	
Periodontitis Bacteria		High Production	Promote CH	Inhibition

The cardiac hypertrophy process is highly complicated that involve many molecular targets, signaling mechanism, transcription factors, genes, effectors, and many enzymes that have a scientifically role in the pathogenicity of this process. Latest research has identified some molecular regulators that have significant role in the betterment of these diseases but still some additional regulatory mechanism and targets needs to be identified. For the treatment of cardiac hypertrophy, future research needs to be utilized this scientific knowledge into potential nutritional and molecular therapies for the betterment of this diseases. We can suppress many gene expression by using the CRISPR/ CAS system. By using all the molecular technologies like RNAi, TALAN, or gene silencing for the inhibition of many gene functions. If we successfully control the regulation of genes, we can almost completely control cardiac hypertrophy and can save people from this disease. The implementation of this scientific knowledge for clinical purposes is major challenges for scientists to exciting about this disease.

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