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Rescue of Familial Hypertrophic Cardiomyopathy by Altering Sarcomeric Exposure and Response to Calcium

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1. Introduction

In 2006, the prevalence of total cardiovascular disease in the US was 81.1 million people, out of which 17.6 million people had coronary heart disease (1). Heart failure, the progressive loss of cardiac contractile performance, affects approximately 5 million Americans, with estimated medical costs of $21-50 billion dollars per year (2). Current pharmacologic therapies focus on symptomatic treatment and halting the progression of the disease (1). Interventional or surgical procedures in the treatment of cardiovascular disease are often restricted to a limited time frame, with heart transplantation patients reliant upon donor hearts that are in great demand.

In recent years, gene therapy studies have made significant progress in the successful treatment of numerous disease conditions using a variety of different approaches. Generally, gene therapy can be classified into two categories: germ line gene therapy where germ cells are modified by the introduction of functional genes which can subsequently be passed on to later generations, and somatic gene therapy where therapeutic genes are transferred into somatic cells of a patient. Another form of gene therapy known as cell-mediated gene therapy is where pluripotent stem cells or progenitor cells are delivered to the injured tissue/organ. The focus of this article will be the modification of disease phenotypes through genetic engineering and transgenic expression of contractile and calcium regulatory proteins.

2. Gene therapy and mouse models of disease

The diseases that were initially targeted for gene therapy were associated with blood disorders or cancers. For example, a decade ago, Pawlink et al demonstrated correction of sickle cell disease in a transgenic mouse model using a β globin gene variant being expressed in a lentiviral vector (3). Hemophilia A was successfully treated in mouse and dog models using adenoviral vectors expressing factor VIII (4). With the great promise of gene therapy in the treatment of disease, the field expanded rapidly with numerous mouse

models having a wide variety of diseases being the target of various therapeutic approaches. For example, mouse models of cystic fibrosis, atherosclerosis, various cancers, and several retinal diseases using different methodological approaches showed great promise for successful treatment (5-10). Cardiovascular diseases have also been treated using gene therapy, targeting defined animal models of cardiac disease. Some of these models of cardiac disease were associated with ischemic heart disease, heart failure, and hypertrophic cardiomyopathy.

Currently, adeno-associated virus vectors are the most potent and promising vectors used for delivery of transgenes to the heart (11, 12). They exhibit efficient uptake, stable long-term expression of transferred genes, and tissue specificity dependent upon the viral serotype (13). Of the 11 identified serotypes of adeno-associated viruses, types 6, 8, and specifically 9, have tropism for the heart (14, 15). In addition to transgenes, these vectors can also deliver microRNAs to the heart which can regulate the simultaneous expression of multiple genes (11).

In this review, we discuss the current studies using *in vivo* models of hypertrophic cardiomyopathy. We describe various mouse models of hypertrophic cardiomyopathy and the different approaches that have been shown to be beneficial in improving cardiac pathology and function. In using these models and testing various therapeutic approaches, a determination of the most effective means for improving cardiomyopathic disease can be elucidated.

3. Familial hypertrophic cardiomyopathy

Familial Hypertrophic Cardiomyopathy (FHC) is a genetic disease caused by autosomal dominant mutations in genes encoding sarcomeric contractile proteins. Hundreds of disease causing mutations in any of 10 genes can result in FHC. These mutations occur in both thick and thin filament proteins, including myosin heavy and light chains, myosin binding protein C, actin, troponins I and T, and α-tropomyosin. Most of these mutations are missense mutations with single amino acid residue substitutions. The overall prevalence of hypertrophic cardiomyopathy is approximately 1 in 500 people; however, many of these individuals exhibit mild symptoms only with late onset in life. Pathologically, FHC is characterized by left and/or right ventricular hypertrophy that occurs in the absence of an increased external load, in addition to intraventricular septal hypertrophy (16). Left ventricular outflow tract obstruction, diastolic dysfunction, and myocyte hypertrophy and disarray are often found. Other common symptoms include myofibrillar disarray and fibrosis, increased calcium sensitivity of myofilaments, and cardiac arrhythmias that may lead to premature sudden death and/or heart failure. An interesting feature is that these symptoms are quite variable, ranging from mild cardiac hypertrophy and no symptoms to marked hypertrophy with diastolic heart failure and sudden death (17). These variable clinical phentoypes strongly suggest that a specific FHC mutation in a contractile protein seemingly can be modified by environmental factors and modifier genes. For example, pathological symptoms associated with FHC mutations in the troponin T gene appear to be minimal; however, most of these patients die of sudden cardiac arrest (18). Patients with FHC mutations in the α-tropomyosin (α-Tm) gene exhibit a wide phenotypic range of symptoms. In the United States, a small percentage (<5%) of FHC patients have mutations in α-Tm with relatively benign symptoms (19). In Japan, the incidence of FHC patients with mutations in α-Tm is still relatively low, but the symptoms are more pathological (20, 21).

Interestingly, in Finland, FHC mutations in the α-Tm gene have a very high incidence rate (11%) among contractile proteins and are a leading cause of FHC; this is most likely due to a "founder's effect" (22). The pathology of FHC with α-Tm mutations is quite severe in the Finnish population with a majority of the patients exhibiting a dramatic phenotype. This variability in incidence and phenotype associated with the Tm cases in different populations most likely reflects environmental factors and modifier genes in altering the onset and pathological symptoms of FHC.

There are 11 mutations in α-Tm that lead to FHC. These mutations are scattered throughout the α-Tm protein, with the majority of them occurring in one of the troponin T binding regions (amino acids 175-190). Since Tm is an α-helical coiled coil protein that dimerizes with itself, and binds to both actin and troponin T, the charge of each specific amino acid residue can play a critical role in both its own structure and in its interaction with its binding partners. In order to gain a greater understanding of the molecular and physiological mechanisms that lead to FHC, we developed 2 transgenic mouse models that incorporate FHC mutations in α-Tm (23-25). Since there is 100% amino acid conservation between mouse and human α-Tm sequence, the FHC mutant α-Tm protein in the transgenic mice is identical to the protein that is found in human patients. The first model entailed a substitution of an asparagine for aspartic acid at codon 175 (Asp175Asn). These mice develop a mild hypertrophic phenotype, coupled with systolic and diastolic dysfunction (23). The cardiac myofilaments demonstrate increased calcium sensitivity, which is in agreement with human studies (26). We also found a correlation between an increase in myofilament calcium sensitivity with a decrease in relaxation rate and a blunted response to β-adrenergic stimulation (27). The second transgenic mouse model was a substitution of glycine for glutamic acid at codon 180 (Glu180Gly) (24, 25). Pathological changes in the hearts of these mice are initially detected by 1 month and include ventricular concentric hypertrophy, fibrosis, and atrial enlargement. These disease-associated changes progressively increase and initially resulted in lethality by 6 months of age; more recently, some of these mice survive much longer probably due to modifying genes introduced when mating the FHC Tm 180 mice with commercial non-transgenic control mice. Physiological analyses show significant alterations in both contraction and relaxation of the heart, with increased sensitivity of the myofilaments to calcium. Isolated cardiomyocytes from the Glu180Gly FHC mice also exhibit an increase in calcium sensitivity of force production (28). Thus, FHC associated Tm proteins alter myofilament structure and properties in individual cardiomyocytes that collectively cause the aberrant function of the entire heart which leads to hypertrophic cardiomyopathy.

4. Rescue of cardiomyopathic mice by contractile proteins

To determine whether it is possible to rescue FHC mice from their lethality and cardiac hypertrophic phenotype, we and others have taken several approaches (29-32). The first approach was to target the myofilaments themselves through the incorporation of proteins that counteract the properties exhibited by the FHC mutant Tm 180 protein since myofilaments obtained from the hearts of FHC patients and animal models usually exhibit an increased sensitivity to calcium with respect to tension development. This is also true for the FHC Tm 180 myofilaments. To compensate for this increased calcium sensitivity, we generated a double-transgenic mouse expressing a chimeric Tm containing the α-Tm amino terminus and the carboxyl terminus of β-Tm, the fetal cardiac isoform (Chi 1) (30). Previous

work demonstrated that myofilaments from these Chi 1 mice have a decreased sensitivity to calcium (33, 34). The double-transgenic mice which were created by crossing the 2 lines displayed normalized myofilament calcium sensitivity. More importantly, the hearts of these mice exhibited a normal morphology with no pathological abnormalities and improved cardiac function (30). These mice also displayed a normal life span. These results demonstrate that alterations in calcium response by modifications in contractile proteins can prevent the pathological and physiological effects of FHC.

Restrictive cardiomyopathy (RCM) is a human condition that displays clinical features of biatrial dilation, a restricted left ventricle, and sudden cardiac death. Patients with this disease have mutations in cardiac z-line proteins, such as desmin and cardiac troponin I and T (35, 36). Recently, a transgenic mouse model was generated (cardiac TnI^{193His}) that displays many of the pathological changes that occur in human patients with RCM, including restrictive ventricles, biatrial enlargement, and sudden cardiac death (37, 38). These mice were crossed with another transgenic mouse line that expresses a cardiac TnI isoform that is truncated at the N-terminus (cTnI-ND) (31, 39); this is a naturally occurring TnI isoform that is found at low levels in normal hearts of all examined species. Transgenic mice expressing the cTnI-ND isoform exhibit a normal cardiac phenotype with no evidence of hypertrophy or histological abnormalites (31). Under hemodynamic stress and heart failure, the cTnI-ND isoform is increased in expression (40). The double transgenic mice (cardiac TnI^{193His} x cTnI-ND) rescued the lethal phenotype of the cardiac TnI^{193His} RCM mutant mice; cardiac function was significantly improved and the myofilaments' increased sensitivity to calcium was reversed (32). These results, which are similar to those found with the FHC Tm180 rescued mice, suggest that calcium desensitization in myofibrils is a therapeutic option for the treatment of diastolic dysfunction.

5. Rescue of cardiomyopathic mice through alterations in calcium handling

In addition to rescuing cardiomyopathic conditions through treatment with compensatory contractile proteins, recent studies have also addressed whether proteins involved with calcium handling can play a role in improving the pathological effects of heart disease. Reports suggest that Serca2a overexpression can modulate cardiac hypertrophy due to removal of calcium from the myofilament region (41-43). To test whether improvements in the hypertrophic phenotype can be achieved through increased Serca2 expression and/or activity, we recently treated the FHC Tm 180 mice with Serca2a, the protein involved in re-sequestering calcium from the cytoplasmic space into the sarcoplasmic reticulum of the cardiomyocyte (44). The approach that we implemented was gene transfer of Serca2a ligated to an adenoviral vector with injection into FHC Tm 180 neonatal hearts. Results demonstrated that a single dose of Serca2a in 1-day-old mice improved the heart morphology, altered hypertrophic gene expression, and improved cardiac function. Histological results showed there was a significant decrease in fibrosis, coupled with a decrease in the heart weight:body weight ratio. Molecular analysis shows that within the first 3 weeks, there is a significant decline in ANF and β-MHC expression in the Serca2a-treated FHC Tm 180 mice. *In situ* hemodynamic measurements show that by 3 months, the hearts from FHC Tm 180 mice treated with Serca2a have significantly improved their response to isoproterenol compared to control mouse hearts. These results demonstrate that gene transfer of a single dose of Serca2a can delay the hypertrophic phenotype and improve cardiac function in an FHC mouse model that is associated with increased myofilament

calcium sensitivity. As such, the study strongly suggests that Serca2a expression should be considered as a potential therapeutic approach in the treatment of FHC.

The benefits for Serca2a overexpression on cardiac function has been demonstrated in both animal models and in human patients. The sodium-calcium exchanger (NCX), along with Serca2a, are the two principle pumps used to remove cytosolic Ca^{2+} in the heart. Both systolic and diastolic improvements occur with more efficient energy usage in removal of Ca^{2+} from the cytosol. Results show that Serca2a removes twice as much cytosolic Ca^{2+} as the NCX for each ATP that is hydrolyzed (12). During heart failure, there is decreased expression and function of Serca2a, which is compensated by increased NCX activity, which is a less efficient energy process. The ratio of Serca2a to NCX changes from approximately 75:25 in the healthy human heart to 50:50 in the failing human heart (45). Normalization of the Serca2a:NCX ratio in heart failure by transgenic or gene therapy approaches appears to hold great therapeutic promise. Studies show that delivery of Serca2a by gene transfer to experimental models of heart failure in sheep and swine can largely reverse cardiac dysfunction and improve systolic and diastolic performance of the heart (46, 47). Recently, percutaneous administration of Serca2a was conducted in phase 1 and 2 clinical studies in humans (48, 49). Heart failure patients were administered an adeno-associated virus expressing Serca2a. Results showed a majority of patients exhibited marked improvements within 6 months, which included improved ejection fraction and end-systolic volume measurements. Thus, the success of these human trials demonstrates that Serca2a may serve as a potential treatment modality for heart failure. Phase 3 clinical trials are expected to be initiated soon.

Another strategy that has been investigated in the treatment of hypertrophic mouse models has been to crossbreed these mice with phospholamban (PLB) knockout mice. PLB is a protein that normally inhibits Serca2a activity of calcium re-sequestration into the sarcoplasmic reticulum. Previous work demonstrated that when a heart failure mouse model due to overexpression of the β-adrenergic receptor was crossed with the PLB knockout mouse, systolic function was improved at 1 year; however, cardiac hypertrophy is still significant (50). In a FHC model of myosin binding protein C, cross-breeding with the PLB knockout mice failed to rescue the hypertrophy, fibrosis and functional parameters of the FHC mutant hearts (51). In a very recent study, we decided to cross the FHC Tm 180 mice with the PLB knockout mice (52). We hypothesized that since Tm is a thin filament protein in the sarcomere, which in FHC primarily affects diastolic function and calcium sensitivity, deletion of PLB may compensate for these altered physiological parameters by increasing the uptake of calcium into the sarcoplasmic reticulum and removing calcium from the myofilament space. Our results demonstrated that PLB ablation in the FHC Tm 180 mice rescued cardiac pathological changes and cardiac function for up to a year (52). The work with Serca2 overexpression and PLB knockout mice suggests that increased Ca^{2+} uptake by the sarcoplasmic reticulum may be a viable target for gene therapy in the treatment of FHC with thin filament contractile protein mutations.

Previous studies from the Metzger laboratory demonstrated that a calcium buffer, parvalbumin, could also play a role in ameliorating some of the FHC Tm180 physiological alterations (53). By crossing a parvalbumin transgenic mouse with the FHC Tm 180 mouse, they demonstrated that the decreased cardiac relaxation that occurs in the FHC mice was corrected. In addition, the relaxation performance was also corrected in cardiomyocytes that were isolated from double transgenic mouse hearts. Similarly, increased levels of parvalbumin expression were also able to rescue a slowed relaxation rate in FHC α-Tm

cardiomyocytes that expressed parvalbumin and the FHC mutant Tm that substituted valine for alanine at codon 63 (53). Thus, these studies reinforce the concept that modification of calcium handling can rescue functional properties of FHC Tm myofilaments.

6. Conclusions

Familial hypertrophic cardiomyopathy is a common disease that is most often associated with mutations in the sarcomeric contractile proteins. Diagnosis and treatment of this condition is still in its infancy, although there have been significant advances in the understanding of the genetic causes of this disease and the molecular pathways that trigger cardiac hypertrophy. Recent studies implicate calcium itself, and the response to calcium by the sarcomere, as playing key roles in the development of hypertrophy. Various methods have been successfully used in animal models of FHC to treat and rescue mice from hypertrophy and heart failure. As such, they have demonstrated a "proof of principle" in the successful treatment of this disease. Some of these treatment methods revolve around re-supplying contractile proteins that counteract the physiological consequences caused by the mutant FHC proteins. For FHC mutations that occur in the thin filament and render the sarcomere most sensitive to calcium, the compensatory protein must exhibit properties associated with a decreased sensitivity to calcium. Other effective treatments focus on removing calcium from the region of the myofilament by enhanced uptake by the sarcoplasmic reticulum or the buffering of calcium. However, considering the large number of genes that activate different molecular pathways in contributing to the hypertrophic phenotype, it is unlikely that a single treatment strategy will be sufficient in addressing the various complexities of this disease. As such, a wide variety of experimental approaches should be pursued so as to design the most effective treatment strategies for the diverse hypertrophic phenotypes that are manifest in human patients.

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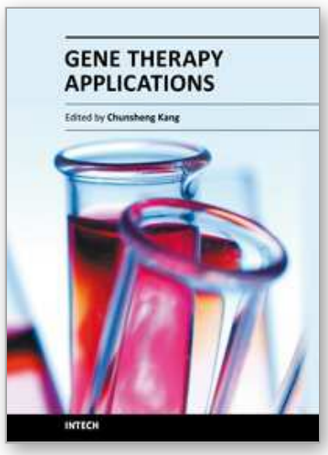

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The aim of our book is to provide a detailed discussion of gene therapy application in human diseases. The book brings together major approaches: (1) Gene therapy in blood and vascular system, (2) Gene therapy in orthopedics, (3) Gene therapy in genitourinary system, (4) Gene therapy in other diseases. This source will make clinicians and researchers comfortable with the potential and problems of gene therapy application.

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