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Therapeutic Strategies Targeting Inherited Cardiomyopathies

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Abstract
Purpose of Review Cardiomyopathies due to genetic mutations are a heterogeneous group of disorders that comprise diseases of contractility, myocardial relaxation, and arrhythmias. Our goal here is to discuss a limited list of genetically inherited cardiomyopathies and the specific therapeutic strategies used to treat them.
Recent Findings Research into the molecular pathophysiology of the development of these cardiomyopathies is leading to the development of novel treatment approaches. Therapies targeting these specific mutations with gene therapy vectors are on the horizon, while other therapies which indirectly affect the physiologic derangements of the mutations are currently being studied and used clinically. Many of these therapies are older medications being given new roles such as mexiletine for Brugada syndrome and diflunisal for transthyretin amyloid cardiomyopathy. A newer targeted therapy, the inhibitor of myosin ATPase MYK-461, has been shown to suppress the development of ventricular hypertrophy, fibrosis, and myocyte disarray and is being studied as a potential therapy in patients with hypertrophic cardiomyopathy.
Summary While this field is too large to be completely contained in a single review, we present a large cross section of recent developments in the field of therapeutics for inherited cardiomyopathies. New therapies are on the horizon, and their development will likely result in improved outcomes for patients inflicted by these conditions.

Keywords Hypertrophic cardiomyopathy · Arrhythmogenic cardiomyopathy · Amyloidosis · Lamin mutations · Hemochromatosis · Fabry's disease · SCN5A mutation · Catecholaminergic polymorphic ventricular tachycardia

Introduction

As we begin to understand the genetic basis for heart disease, more specific therapies are being developed. In the case of genetically inherited cardiomyopathies, therapies that target specific aspects of these diseases are being actively researched and developed. Specific targeted therapies are those that counteract the specific molecular derangement caused by the genetic mutation. The goal of this review is to look at a variety of genetically inherited syndromes that have cardiac involvement and treatments used in their specific instances. There are too many types and subtypes of inherited cardiomyopathies with specific treatments to discuss in one review. Many reviews are dedicated to the pathophysiology and specific treatments for one specific syndrome. Thus, this will be merely a sample of current therapy and therapies on the horizon.

SCN5A Mutations

The SCN5A gene encodes for a voltage-gated sodium channel involved in myocardial electrical conduction and the rapid upstroke of the action potential. It is the predominant isoform in the heart. Mutations in the gene can play a causative role in

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malignant arrhythmia syndromes such as type III long-QT syndrome (LQT3), Brugada syndrome [1], and even dilated cardiomyopathy [2]. A specific subgroup of idiopathic ventricular fibrillation later named Brugada syndrome was first described in 1992 [3]. Several years later, various types of mutations in the SCN5A gene were found to be present in families with a history of Brugada syndrome [4]. Around that same time, a linkage was discovered between genetic polymorphisms within the SCN5A gene and LQT3 [5].

The mechanisms by which these mutations cause these syndromes were not elucidated until the early 2000s. In 2002, Baroudi et al. reported that SCN5A mutations R123W and T1620M, responsible for the Brugada syndrome, resulted in the absence of channel function due to disruption in channel trafficking toward the plasma membrane [6]. That same year, the SCN5A mutation M1766L was discovered in an infant with prolonged QT syndrome type III and torsades de pointes. This mutation caused a decrease in sodium current measured in HEK cells that improved with mexiletine [7]. In 2004, Valdivia et al. reported that mexiletine rescued the membrane expression of the voltage-gated sodium channel in HEK cells expressing the Brugada syndrome mutation G1743R by somehow acting as a molecular chaperone helping to transport the protein from the sarcoplasmic reticulum to the plasma membrane [8]. This rescue mechanism of mexiletine was supported by Tan et al. who reported that the Brugada syndrome-associated mutation, G1406R, also displayed a trafficking defect rescued by mexiletine [9]. Pfahnl et al. showed that the Brugada syndrome causing the T353I mutation produced a failure to transport the protein to the sarcolemma resulting in decreased expression. However, while mexiletine rescued the trafficking defect and restored the membrane expression to near-normal levels, the electrical current pattern included a significant late current consistent with a long-QT syndrome phenotype [10]. This effect was also seen by Ruan et al. who reported in 2010 that the SCN5A mutation F1473S (associated with long-QT syndrome type III in a child) resulted in reduced expression of the voltage-gated channel. While expression of the sodium channel was improved with mexiletine, the drug resulted in further prolongation of the already QT prolongation [11].

Most recently, Mazzanti et al. showed that mexiletine could shorten the QTc interval in patients with LQT3 mutations. In a non-randomized prospective study, 36 patients with LQT3 were given mexiletine. They found a reduction in the annual rate of arrhythmic events from 10.3 to 0.7% [12•]. The use of sodium channel blockers in LQT3 syndrome patients is also supported by the most recent ESC clinical guidelines [13].

Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a condition characterized by episodic polymorphic ventricular tachycardia brought on by any state that causes a heighted catecholaminergic state [14]. CPVT has been found to be associated with mutations in the ryanodine receptor [15, 16] (RyR2), calsequestrin [17] (CASQ2), triadin [18] (TRDN), and calmodulin [19] (CALM1) and is considered generally to be a disorder of calcium handling in the individual myocytes with mutations. Specifically, these mutations cause an increase in delayed after-depolarization from spontaneous calcium release from the sarcoplasmic reticulum [20]. The gene KCNJ2 coding for an inwardly rectifying potassium channel may be associated with CPVT, though this remains controversial [21, 22]. Of these mutations, the autosomal dominant inherited mutations in RyR2 are the most common (around 60%) [22, 23], and may even explain a significant number of unexplained cases of sudden cardiac death in patients not previously diagnosed with CPVT [24]. Loss-of-function mutations in CASQ2 are autosomal recessive and account for far fewer cases. These mutations are thought to cause arrhythmia through a similar mechanism as the RyR2 mutations [25].

While most patients who have recurrent ventricular tachycardia assessed to be CPVT get implantable cardioverter defibrillators (ICD), more specific therapies are being employed to prevent recurrence and minimize ICD shocks. Given its association with a heightened catecholaminergic state, the use of beta blockers is the mainstay of therapy and has been shown to be associated with a lower rate of arrhythmia [26]. Nadolol is frequently chosen because it is long acting and has no intrinsic sympathomimetic activity. The use of nadolol over β1 selective beta blockers such as metoprolol succinate has been shown to provide great efficacy at reducing the rate of exercise-induced arrhythmias [27].

In patients who have arrhythmias refractory to beta blocker and activity avoidance, the use of flecainide has been proposed as a viable therapeutic agent. While flecainide is best known as a class 1C sodium channel blocker, it also can inhibit cardiac RyR2 calcium release acting to help prevent the calcium flux-associated polymorphic ventricular tachycardia [28, 29]. The addition of flecainide to the regimen of 33 patients with CPVT suppressed 76% of exercise-induced ventricular arrhythmias [30•]. Even patients determined to have CPVT without an identifiable mutation culprit seem to benefit from flecainide by reducing exercise-induced arrhythmias [31]. Specific cases of patients who have been refractory to calcium channel blocker and beta blocker therapy and with defibrillator-induced storming of ventricular tachycardia rescued with flecainide have been reported [32, 33]. The mechanism by which flecainide prevents arrhythmias in patients

with CPVT is not fully elucidated. It may be a direct effect on the RyR2 receptor [34, 35], or it may act through its antagonistic activity on voltage-gated sodium channels by increasing the threshold for triggered activity [20, 36, 37]. Finally, patients with calsequestrin-associated CPVT (denoted CPVT2) may also benefit from flecainide by preventing exercise-induced polymorphic VT [38]. While there is little controversy as to the beneficial effects of flecainide in patients with CPVT, the exact anti-arrhythmic mechanism has not been fully established.

In patients who have contraindications or are refractory to medical therapy, left cardiac sympathetic denervation is also an option. This was first described in three patients with medication-refractory CPVT with excellent results [39]. Since then, only single-center trials and low numbers of CPVT patients have been reported, some with good [40–42] some with less certain results [43] or with good results but short-term follow-up [44].

Future therapeutics under study include JTV-519, an experimental drug that decreases intracellular calcium leak via the RyR2, which may be a viable option for patients with CPVT-causing mutations in the future. This was initially shown from biochemical experiments [45] and later in dilated murine ventricular myocytes harboring a CPVT RyR2 mutation [46]. Most recently, a related compound that decreases intracellular calcium leak, EL9, was shown to reduce ventricular tachyarrhythmias in mice carrying a CPVT-causing RyR2 mutation [47].

Transthyretin Amyloid Cardiomyopathy

Transthyretin amyloid cardiomyopathy is a condition of amyloid involvement in the myocardium and can lead to heart failure (with preserved or reduced ejection fraction), a restrictive phenotype, and atrial arrhythmias [48, 49]. Patients carrying certain mutations of the transthyretin (TTR) gene have a high risk of developing familial amyloid cardiomyopathy. This is secondary to decreased stability of the TTR tetramer which results in amyloid deposition. The V122I mutation is a common one found in 3–4% of African Americans [50]. In the Transthyretin Amyloidosis Cardiac Study, patients carrying the V122I mutation who were diagnosed with amyloid cardiomyopathy had a median survival from diagnosis of 25.6 months [51]. Definitive treatment for TTR cardiac amyloidosis in the past has been limited to heart transplant, liver transplant, or a combination of the two [48].

Tafamidis meglumine (tafamidis; Pfizer Inc.; New York, NY) is a novel compound being studied that targets the thyroxin binding site of the TTR tetramer and inhibits its dissociation [52]. This compound has been used to treat familial amyloid polyneuropathy in Europe and can delay neurological impairment [53]. Recently, there have been published studies on the effects of tafamidis in wild-type TTR cardiac amyloidosis. Maurer and colleagues published the effects of tafamidis on transthyretin stabilization and clinical outcomes in a phase 2 open-label trial. The trial included 31 patients NYHA class I–II with wild-type TTR amyloid cardiomyopathy who received 20 mg daily of tafamidis for 12 months. At 6 weeks, almost all patients achieved TTR stabilization as determined by an immunoturbidimetric assay. There were no clinically significant changes in the echocardiogram parameters at 12 months compared to the start of the study. Fifteen of 31 patients had progression of disease as determined by a rise in NT-proBNP >1000 pg/mL, an increase in serum creatinine of ≥0.5 mg/dL, or a >50 m decline in distance walked in the 6-min walk test during the 12 months taking 20 mg of tafamidis. The study was designed to evaluate TTR stabilization which was achieved, but larger studies will need to be done to assess efficacy [54]. Damy and colleagues also performed a study on 21 patients with non-Val30Met and non-Val122Ile hereditary TTR cardiac amyloidosis administering tafamidis 20 mg per day for 12 months. In this small open-label study, there were no clinically relevant changes in the mean echocardiographic or electrocardiographic variables. There were no safety concerns [55, 56]. In patients with the Val30Met TTR mutation, tafamidis was found to lead to stabilization of cardiac biomarkers and echocardiographic parameters [57].

Other potential targeted treatments include diflunisal and doxycycline. Diflunisal is a non-steroidal anti-inflammatory drug which has been shown to stabilize the TTR tetramer and has been proposed as a treatment for the manifestations of TTR amyloidosis [58]. A preliminary study on the use of diflunisal in patients with TTR amyloidosis shows that it is well tolerated. In this 13-patient study that lasted about 1 year, there was no significant change in cardiac mass, ejection fraction, troponin I, or BNP [59]. Larger studies need to be performed for the statistical power to determine if diflunisal is a viable treatment modality. Doxycycline when combined with tauroursodeoxycholic acid was associated with no progression of cardiomyopathy during treatment in a small 20-patient phase II trial [60].

Interfering RNA (RNAi) therapy is an emerging strategy that aims to reduce hepatic production of transthyretin by interfering with translation. In a recent phase I placebo-controlled trial, a small RNAi delivered in lipid nanoparticles was studied in 32 patients with TTR amyloid and 17 healthy volunteers over the course of 28 days. Most of these patients harbored the V30M mutation, which causes polyneuropathy and less so cardiomyopathy. However, the concept would presumably be valid with any mutation or even wild-type TTR amyloid cardiomyopathy. In this study, significant reduction in serum transthyretin levels was observed with only mild to moderate infusion-related reactions. Clinical endpoints were not examined [61•].

Hemochromatosis

Iron overload cardiomyopathy is frequently secondary to hereditary hemochromatosis. Most cases are caused by mutations in the HFE gene leading to elevated total body iron that subsequently gets deposited in the myocardium leading to myocardial damage. Clinically, patients may be initially characterized by diastolic dysfunction and restrictive hemodynamics and later (as the disease progresses) develop a dilated cardiomyopathy with reduced ejection fraction [62]. The mainstay of treatment is removal of excess iron from the tissues, preventing myocardial damage with early intervention being the goal. Regular phlebotomy disposes excess iron and has been shown to improve echocardiographic parameters of LV wall thickness and function [63, 64]. However, this is not a treatment option in patients with anemia. Moreover, it is not an option for those with severe congestive heart failure.

Chelation therapy is an option for those with anemia or with more advanced cardiac disease. Three medications, deferoxamine, deferiprone, and deferasirox, are all approved by the Food and Drug Administration. Most of the data on iron chelation and improvement of myocardial iron overload is in transfusion-dependent thalassemia patients. Deferoxamine has been shown to reduce the risk of developing cardiac disease [65] and improve systolic function in patients with iron overload, secondary to chronic transfusion [66, 67]. Deferiprone and deferasirox are alternative chelating agents whose efficacy and long-term safety data are not as well established as deferoxamine [68].

Anderson Fabry's Cardiomyopathy

Anderson Fabry's disease results from a genetic deficiency in the enzyme alpha galactosidase A which results in globotriaosylceramide accumulation. It is the second most prevalent lysosomal storage disease second only to Gaucher's disease. It is an X-linked condition that results in progressive problems in many systems including renal insufficiency and stroke, and it can result in hypertrophic cardiomyopathy [69]. In a review of 279 male and 168 female Fabry's patients, cardiac arrhythmia was seen in 42% of male patients and 27% of female patients, angina 13 and 14% of male and female patients, respectively, and heart failure was seen in 4 and 1% of the male and female patients, respectively [70].

Prior to the development of enzyme replacement therapy, no specific treatments were available. The two current options include agalsidase alpha (Replagal) and agalsidase beta (Fabrazyme). Early studies showed that enzyme replacement therapy seemed to be safe but and also decreased the deposits of globotriaosylceramide in the liver and renal tubular cells [71] as well as deposits in the skin and myocardial tissue [72, 73]. Soon after the initial safety study, it was found that echocardiographic parameters of left ventricular size and function (quantified by strain pattern) improved in patients with Fabry's disease treated with enzyme replacement therapy for 12 months [74]. In 2007, Banikazemi published a study on 82 Fabry's disease patients who received agalsidase beta or placebo over 35 months. The composite clinical outcome of renal, cardiac, and cerebrovascular complications and death were mitigated, though there was no significant difference in cardiac events between the groups [75]. Treatment of 181 adult Fabry patients with agalsidase alpha showed that, in patients with baseline cardiac hypertrophy, treatment resulted in a reduction in the left ventricular mass index after 5 years. Patients without baseline hypertrophy remained stable [76•]. Furthermore, when patients without advanced cardiomyopathy were treated with enzyme replacement, reduced left ventricular mass and improved myocardial function and exercise capacity were observed after 3 years of treatment [77]. In a clinical trial of 58 patients who received 1 mg/kg of agalsidase beta every 2 weeks over a 10-year period, the left ventricular posterior wall thickness and interventricular septum thickness did not show a significant increase over the treatment period and remained normal [78]. Despite enzyme replacement therapy, cardiac complications are now the primary cause of death in both male and female Fabry's patients (surpassing renal disease) regardless of whether they receive enzyme replacement therapy or not [79].

Hypertrophic Cardiomyopathy

Mutations in sarcomeric proteins account for about 65% of all cases of hypertrophic cardiomyopathy [80]. Over 400 familial hypertrophic cardiomyopathy mutations have been identified [81]. The mutations can occur in many sarcomeric proteins on both the thin and thick filament, and most of them occur in myosin and myosin binding protein C [81, 82]. The discussion below pertains to targeted treatments for familial hypertrophic cardiomyopathy.

Losartan is an angiotensin II receptor blocker (ARB) used primarily to treat hypertension. In 2007, Yamazki et al. performed a small study in 19 patients with hypertrophic non-obstructive cardiomyopathy where patients were treated with 50 mg of losartan or placebo and left ventricular mass was assessed by MRI. The study showed that left ventricular mass reduced by a ratio of 0.93 compared to 1.02 for placebo [83]. A similar study of 20 patients showed that 50 mg of losartan produced a non-significant ($p = 0.06$) change in LV mass in patients with non-obstructive hypertrophic cardiomyopathy compared to placebo [84]. The ARB candesartan was also examined. In a randomized double-blinded study of 24 patients with non-obstructive hypertrophic cardiomyopathy, after 1 year and using 32 mg as a target dose, there was a significant regression of left ventricular hypertrophy,

improvement in left ventricular function (assessed by echocardiography), and improvement of exercise tolerance. The patients who had the largest regression of hypertrophy were those who carried beta myosin heavy chain mutations [85]. However, the findings of these smaller studies were not corroborated in a larger trial. The INHERIT trial studied losartan 100 mg in a randomized, double-blinded, placebo-controlled fashion in 133 patients with obstructive and non-obstructive hypertrophic cardiomyopathy and found no change in left ventricular mass assessed by cardiac MRI or CT [86]. The VANISH study (Valsartan for attenuating disease evolution in early sarcomeric HCM) is currently recruiting participants (NCT 01912534) [87]. More studies will need to be done in the future, potentially using ARBs other than losartan to help answer the question of their role in hypertrophic cardiomyopathy.

Aldosterone has also been implicated in the pathogenesis of inherited hypertrophic cardiomyopathy. In mice carrying the hypertrophic cardiomyopathy-associated troponin T Q92 mutation, antagonizing aldosterone with spironolactone reversed myocardial fibrosis, attenuated myocyte disarray by 50%, and improved diastolic function [88].

Augmenting sarcoplasmic reticulum (SR) calcium uptake by augmenting gene expression of the SERCA2a calcium pump has also been speculated to be a mechanism by which the hypertrophic cardiomyopathy phenotype can be altered. Using a transgenic mouse model of familial hypertrophic cardiomyopathy with a mutation in tropomyosin, Pena et al. showed that over-expression of SERCA2A improved overall whole heart morphology and augmented contractility and response to isoproterenol [89]. SR calcium reuptake can also be augmented by phosphorylation of the SERCA2 inhibitor phospholamban. The augmentation of SR calcium uptake hypothesis was corroborated when the tropomyosin mutant mice were crossed with the phospholamban knockout mouse. These mice displayed improved ventricular function and less collagen deposition compared to the mice with the tropomyosin mutation only [90].

While intracellular calcium handling has been a genetic target for hypertrophic cardiomyopathy, blocking the L-type calcium channel with diltiazem has also been studied. In 2002, Semsarian et al. showed that in transgenic mice bearing the Arg403Gln missense mutation in the alpha cardiac myosin heavy chain, SR calcium, SR calsequestrin, and SR ryanodine receptor levels were reduced prior to the development of pathologic changes seen in myocardial structure. Furthermore, early use of diltiazem restored the expression of calsequestrin and the ryanodine receptor and prevented the development of the myocardial hypertrophy and myocyte disarray [91]. Using a transgenic mouse with the hypertrophic cardiomyopathy-associated troponin T I79N mutation, Westermann et al. showed that pre-treatment with diltiazem prevented the development of severe diastolic dysfunction in these mice [92]. Diltiazem was also shown to improve peak early diastolic velocity as assessed by echocardiography in a small group of patients who were carriers for a mutation in cardiac myosin binding protein C mutation, but did not show evidence of hypertrophy yet. It was speculated that diltiazem might help prevent development of later structural changes in hypertrophic cardiomyopathy [93]. Most recently, a randomized double-blinded study of 38 patients who carried sarcomere mutations was performed where patients received either diltiazem or placebo for a median of 25 months. The results showed that left ventricular end-diastolic diameter and left ventricular wall thickness improved in the diltiazem group, but worsened in the placebo group [94]. Further studies will need to be completed to determine the long-term efficacy in treating this patient population.

Increased myofilament calcium sensitivity is thought to be one of the mechanisms of hypertrophic cardiomyopathy [81]. Therefore, treatments aimed at decreasing myofilament calcium sensitivity have been postulated as potential strategies. Small-molecule inhibitors of cross-bridge formation, one example being blebbistatin, specifically inhibit actin-myosin interaction [95]. The only studies looking at blebbistatin are in animal models. For example, Baudenbacher et al. showed that blebbistatin could reduce arrhythmia susceptibility in a mouse model of hypertrophy with a troponin T mutation [96]. Coutu et al. overexpressed parvalbumin (a calcium-buffering compound) in mouse models of hypertrophic cardiomyopathy with a mutation in tropomyosin and found that the enhanced intracellular calcium buffering leads to improved diastolic function [97]. Strategies to develop therapies for inherited hypertrophic cardiomyopathy are actively ongoing. Their compound MYK-461 acts as an inhibitor of myosin ATPase by decreasing the steady-state rate of the ATPase activity [98]. The molecule is being studied as a part of a phase I clinical trial (NCT02329184). Using a transgenic mouse model with a mutation in the myosin heavy chain that develops hypertrophic cardiomyopathy, Green et al. showed that MYK-461 suppressed the developed ventricular hypertrophy, fibrosis, and myocyte disarray, further supporting the notion that inhibiting hyperdynamic contraction may be of therapeutic benefit in patients with hypertrophic cardiomyopathy [99•].

Intracellular sodium fluxes have also been a focus of treatment for hypertrophic cardiomyopathy. Using human myocytes obtained from myectomy operations, Coppini et al. showed that these myocytes exhibit a prolonged action potential related to increased late sodium current that led to prolonged plateau phase calcium current which resulted in augmented calcium calmodulin kinase II activity. Ranolazine is an antagonist to the late sodium current at therapeutic levels [100]. The drug was able to reduce acceleration of the contraction and relaxation cycle of HCM trabeculae [101]. A recent study conducted by Flenner et al. showed that

ranolazine improved tolerance to high work load in mice with Mybpc3-targeted knock out in mice with hypertrophic cardiomyopathy. However, the mechanism of this was antagonizing the beta adrenergic receptor. In addition, 6 months of treatment with ranolazine did not reverse the cardiac hypertrophy or dysfunction in vivo [102]. The RHYME (ranolazine for treatment of angina or dyspnea in hypertrophic cardiomyopathy patients) trial demonstrated some improved symptoms and quality of life in a small 14-patient study [103]. There is a multicenter, double-blind, placebo-controlled study underway to assess the effects of ranolazine on exercise capacity, diastolic function, and symptoms in patients with hypertrophic cardiomyopathy (The RESTYLE-HCM, EUDRA-CT 2011-004507-20) which should provide more clear answers to the question of ranolazine in this disease. Electazine (GS 6615) is another inhibitor of the late-phase sodium current originally designed for patients with LQT3 syndrome that was studied as a means to improve exercise capacity in patients with symptomatic hypertrophic cardiomyopathy (LIBERTY-HCM NCT02291237) [104]. This trial was recently terminated for reasons that are not entirely clear at the time of this writing.

N-Acetylcysteine has been studied as a possible therapeutic agent in hypertrophic cardiomyopathy. In a study in 2004 by Marian et al., transgenic mice carrying the hypertrophic cardiomyopathy-associated troponin T Q92 mutation were treated with *N*-acetylcysteine. They found that *N*-acetylcysteine reduced myocardial fibrosis [105]. This finding was supported in 2009 by Lombardi et al. who showed that in a rabbit model of hypertrophic cardiomyopathy and beta myosin heavy chain mutation Q403, treatment with *N*-acetylcysteine reversed cardiac and myocyte hypertrophy and interstitial fibrosis, reduced the propensity for ventricular arrhythmias, and prevented cardiac dysfunction [106]. This hypothesis was further corroborated when Wilder et al. showed that administration of *N*-acetylcysteine for 30 days to transgenic mice expressing the hypertrophic cardiomyopathy-associated tropomyosin mutation Tm-E180G reversed the baseline diastolic dysfunction and hypertrophy [107]. A clinical trial to test its potential benefit on hypertrophic cardiomyopathy patients is at the recruiting stage (NCT01537926).

Lamin Mutations Dilated Cardiomyopathy

Lamin A and C are filament proteins of the nuclear envelope, encoded by the same gene (LMNA), that have structural function in the nuclear membrane and are involved in transcriptional regulations [108, 109]. Ever since Bonne et al. published that mutations in the gene encoding lamin A/C caused Emery-Dreifuss muscular dystrophy which can result in a dilated cardiomyopathy with conduction system disease, it has been known that lamin A/C mutations have a link to inherited cardiomyopathies [110]. The prevalence of LMNA mutations in families with inherited dilated cardiomyopathy has been estimated at 8% [111].

Currently, there are no approved treatments for LMNA mutation-associated dilated cardiomyopathy other than standard evidence-based therapies all other patients with dilated cardiomyopathy should receive. Animal studies have given us insight into what future treatments might target. Enhanced p38alpha signaling has been discovered in the hearts of mice with dilated cardiomyopathy harboring an LMNA mutation and implemented in the pathophysiology. Using the P38 alpha inhibitor AARY-371791, Muchir et al. treated mice with LMNA mutation-associated dilated cardiomyopathy and found that LV dimensions and fractional shortening improved [112]. Improvement in cardiac function was shown in other LMNA mutations, again in mouse models. Preventing apoptosis is a proposed mechanism of action for how p38 inhibition improves heart function in mice with LMNA mutations. Currently, AARY-371791 is undergoing a phase II clinical trial in patients with LMNA mutation dilated cardiomyopathy (NCT 02057341).

Conclusions

Inherited cardiomyopathies represent a rarer slice of cardiovascular disease when compared to conditions with a mixture of genetic and non-genetic risk factors such as coronary artery disease and atrial fibrillation. As such, targeted therapies for these conditions have been slower in development. The keys to treating some of these conditions lay in the rebranding of older medications for these new uses and in other cases the development of novel agents used to target the molecular derangements resulting from genetic mutations. New therapies and therapeutic strategies are on the horizon, and their development will likely result in improved outcomes for patients inflicted by these conditions.

Compliance with Ethical Standards

Conflict of Interest Kenneth Varian declares no conflict of interest.

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