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Cell signaling abnormalities in cardiomyopathy caused by lamin A/C gene mutations

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Author Contribution

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Abstract

Mutations in the lamin A/C gene (*LMNA*) encoding intermediate filament proteins associated with the inner nuclear membrane cause diseases known as laminopathies. Most *LMNA* mutations cause dilated cardiomyopathy with variable skeletal muscular dystrophy. Cell signaling abnormalities have been discovered in hearts of mouse models of cardiomyopathy caused by *LMNA* mutations that contribute to pathogenesis. These include abnormally increased signaling by extracellular signal-regulated kinase 1 and kinase 2 and other mitogen-activated protein kinases, protein kinase B/mammalian target of rapamycin complex 1 and transforming growth factor-β. Preclinical research suggests that specific inhibitors of these abnormally activated cell signaling pathways may be useful in treating human patients with this disease.

Introduction

The human lamin A/C gene (*LMNA*) encodes prelamin A, which is processed to lamin A, and lamin C [1]. Lamin A, lamin C and B-type lamins have structural similarity to intermediate filament proteins, but assemble into tetrameric filaments of 3.5 nm thickness at the inner aspect of the inner nuclear membrane in somatic cells [2–4]. Lamins interact with several integral proteins concentrated in the inner nuclear membrane as well as various nucleoplasmic proteins [5].

A-type lamins are expressed in most terminally differentiated cells. However, mutations in *LMNA* cause inherited diseases called laminopathies that are organ system selective. These can be broadly separated into disorders that primarily affect either (1) striated muscle, (2) adipose tissue, (3) peripheral nerve or (4) multiple organ systems usually with features of accelerated aging [6]. Among the laminopathies affecting striated muscle with onset from childhood to adulthood are Emery–Dreifuss muscular dystrophy, isolated dilated cardiomyopathy, a form of limb–girdle muscular dystrophy or variants of these entities that were originally defined based on clinical features [7–11]. Some *LMNA* mutations also cause a congenital muscular dystrophy presenting in very early childhood [12,13]. The inheritance pattern is almost always autosomal dominant, but rare compound heterozygous mutations have been described. The common and life-threatening feature of laminopathies primarily affecting striated muscle is dilated cardiomyopathy, which is generally associated with early onset atrioventricular conduction block. Cardiomyopathy caused by *LMNA* mutations has a relatively rapidly progressive course with sudden death from arrhythmias and the onset of heart failure occurring at earlier ages than most other inherited cardiomyopathies [14,15].

Signaling pathway abnormalities in cardiomyopathy caused by *LMNA* mutations

Several mouse lines have been generated with mutations in the lamin A/C (*Lmna*) gene. We have utilized $Lmna^{H222P/H222P}$ mice generated by Arimura et al. [16] to examine abnormalities in cell signaling pathways in the heart. These mice recapitulate most features of cardiomyopathy seen in humans with *LMNA* mutations; however, with the caveat that the mice are homozygous for the *Lmna* mutation, whereas in humans the disease is almost always dominant.

Bioinformatics analyses of transcriptomes from hearts of male $Lmna^{H222P/H222P}$ mice at 10 weeks of age, which is when symptoms of cardiomyopathy first appear, suggested abnormalities in several signaling pathways [17–19]. Prominent among these were mitogen-activated protein kinase (MAP kinase), protein kinase B (AKT)/mammalian target of rapamycin complex 1 (mTORC1) and transforming growth factor-β (TGF-β) signaling. TGF-β signaling had previously been shown to be hyperactivated in the original description of $Lmna^{H222P/H222P}$ mice [16]. WNT/β-catenin signaling was also suggested to be altered.

Biochemical interrogation of heart tissue from $Lmna^{H222P/H222P}$ mice showed that among the MAP kinase cascades, c-Jun N-terminal kinase (JNK), p38α and extracellular signal-regulated kinases 1 and 2 (ERK1 and 2) were all hyperactivated [17–19]. Biochemical experiments also confirmed hyperactivation of the AKT/mTORC1 pathway [20]. Other investigators also showed mTORC1 signaling hyperactivation in hearts of $Lmna^{-/-}$ mice that develop cardiomyopathy at a younger age [21]. The abnormal increases in AKT/mTORC1 signaling were linked to decreased macroautophagy (autophagy) in heart muscle. ERK1/2 and AKT/mTORC1 signaling are hyperactivated in hearts of male $Lmna^{H222P/H222P}$ mice as early as 4 weeks of age, which is prior to

the onset of any detectable pathology [17,20]. WNT/β-catenin signaling was later shown to be decreased in hearts of *Lmna*$^{H222P/H222P}$ mice starting at ~12 weeks of age in male mice [22]. Similar alterations in ERK1/2, AKT/mTORC1, TGF-β and WNT/β-catenin signaling have been demonstrated in hearts from humans with cardiomyopathy caused by *LMNA* mutations, although tissues have only been available at late-disease stages [20,22,23,24]. Female *Lmna*$^{H222P/H222P}$ mice have a later onset of disease and, for practical purposes, were not used in most of these experiments; however, a research in progress has shown similar defects in ERK1/2 and AKT activities but at older ages.

Connecting signaling abnormalities to pathology

Given the abnormal elevations in MAP kinase, AKT/mTORC1 and TGF-β signaling in hearts of *Lmna*$^{H222P/H222P}$ mice, we hypothesized that reducing them would have beneficial effects on cardiac function. If so, it would link these cell signaling defects to cardiac pathology. We initially tested PD98059, one of the first synthetic inhibitors of mitogen-activated protein kinase kinases 1 and 2 (MEK1/2), the enzyme upstream of ERK1/2 that activates it by phosphorylation [25]. The treatment of male *Lmna*$^{H222P/H222P}$ mice with PD98059 starting at 8 weeks of age, prior to the onset of significant cardiac dysfunction, reduced ERK1/2 phosphorylation and delayed the development of left ventricular dilatation. At 16 weeks of age, the drug-treated mice demonstrated normal left ventricular ejection fraction, whereas the placebo-treated mice demonstrated a 30% reduction. We similarly treated male *Lmna*$^{H222P/H222P}$ mice starting at 8 weeks of age with SP600125, an inhibitor of all mammalian isoforms of JNK [26]. Treatment with SP600125 inhibited JNK phosphorylation in the heart with no detectable effect on ERK1/2, delayed the development of left ventricular dilatation, prevented decreases in cardiac ejection fraction and decreased fibrosis at 16 weeks of age.

Perhaps more relevant to potential treatment of human subjects is the benefit of blocking ERK1/2 or JNK activity after the onset of detectable cardiac dysfunction. Unless their preventive effects were exceptionally powerful, it would be imprudent to use such drugs as prophylactic treatment in asymptomatic humans with *LMNA* mutations. We, therefore, treated male *Lmna*$^{H222P/H222P}$ with PD98059 or SP600125 to respectively reduce ERK1/2 or JNK signaling, starting at 16 weeks of age when they already have decreased left ventricular fractional shortening. Treatment with either of these inhibitors led to decreased left ventricular end-systolic dilatation and increased left ventricular ejection fraction after 4 weeks of treatment compared with mice receiving placebo [27]. There was also a decrease in cardiac fibrosis compared with placebo-treated mice. Notably, fibrosis is prominent in cardiomyopathy caused by *LMNA* mutations, which not only contributes to left ventricular stiffness, but at earlier stages may underlie the development of atrioventricular conduction block and ventricular arrhythmias [28–31].

We next tested if the inhibition of p38α signaling would have impact on the deterioration of left ventricular function in *Lmna*$^{H222P/H222P}$ mice. We blocked p38α signaling using ARRY-371797, an orally available inhibitor of p38α. After the treatment for 4 weeks in male *Lmna*$^{H222P/H222P}$ mice starting at 16 weeks of age, ARRY-371797 reduced phosphorylated p38α in hearts that was associated with significantly decreased left ventricular diameters and increased left ventricular fractional

shortening compared with placebo [19]. However, ARRY-371797 did not significantly reduce the expression of genes encoding collagens, suggesting that it did not have a major effect on cardiac fibrosis. Nonetheless, this study showed that abnormally increased p38α signaling contributed to cardiac pathology in *Lmna*$^{H222P/H222P}$ mice.

We and others also tested the effects of inhibitors of mTORC1 activity in mouse models of cardiomyopathy caused by *LMNA* mutations. In a trial lasting only 2 weeks, treatment of male *Lmna*$^{H222P/H222P}$ mice with the rapamycin analog temsirolimus starting at 14 weeks of age after the onset of cardiac pathology reduced phosphorylated mTOR, a protein kinase component of mTORC1, in hearts; this was associated with significantly smaller left ventricular diameters and significantly increased left ventricular fractional shortening compared with mice treated with placebo [20]. In this short-term experiment, however, the expressions of genes encoding collagens and fibronectin involved in fibrosis were not reduced. Treatment with an MEK1/2 inhibitor also reduced phosphorylation of mTOR in hearts of *Lmna*$^{H222P/H222P}$ mice, suggesting that ERK1/2 hyperactivation contributes to increased mTORC1 signaling. Rapamycin treatment of *Lmna*$^{-/-}$ mice, which have a median survival of only 6–8 weeks and develop heart disease early in life, had beneficial effects on heart function and prolonged survival [21]. Temsirolimus and rapamycin also partially reversed the reduction in autophagy in heart muscle of these *Lmna* mutant mice, correlating defects in this cellular process with cardiac pathology [20,21].

Given the enhanced TGF-β signaling in hearts of *Lmna*$^{H222P/H222P}$ mice and its known role in fibrosis, we tested if reducing its signaling activity would attenuate myocardial fibrosis and improve cardiac function. We treated male *Lmna*$^{H222P/H222P}$ mice with SB-431543, an inhibitor of the TGF-β type I receptor kinase, starting at 16 weeks of age. After 4 weeks of treatment, these mice had reduced myocardial fibrosis along with decreased left ventricular diameters and increased left ventricular fractional shortening compared with mice treated with placebo [24]. The treatment of *Lmna*$^{H222P/H222P}$ mice with an MEK1/2 inhibitor also led to a decrease in nuclear phosphorylated Smad2 and Smad3, mediators of TGF-β signaling, compared with placebo-treated mice. This suggests that hyperactivation of ERK1/2 signaling contributes to TGF-β-mediated myocardial fibrosis in *Lmna*$^{H222P/H222P}$ mice.

Toward drug therapy for cardiomyopathy caused by *LMNA* mutations

The work on cell signaling abnormalities in cardiomyopathy caused by *LMNA* mutations provides a starting point for human clinical investigation. However, there are several large steps from experimental studies in genetically modified mice to human therapy. While the mTORC1 signaling inhibitors rapamycin and temsirolimus are used clinically in human subjects for different indications, the MAP kinase and TGF-β inhibitors used in the studies described above are not all ideal drug candidates. Only ARRY-371797 is currently in active clinical development.

Most of the studies described above have been relatively short term and used relatively small numbers of mice. The most extensively studied class of drugs for this inherited cardiomyopathy in model mice has been the MEK1/2 inhibitors that reduce ERK1/2 activity. Multiple studies with different drugs in this class have shown reproducible improvements in left ventricular

function, decreased cardiac fibrosis and prolonged survival in *Lmna*$^{H222P/H222P}$ mice [23,25,27,32]. One of these utilized selumetinib, an MEK1/2 inhibitor, currently in advanced clinical trials for cancer [23]. More recently, we have shown that CIP-137401, a novel macrocyclic preclinical MEK1/2 inhibitor with excellent drug-like properties, appears safe, improves left ventricular function, decreases cardiac fibrosis and prolongs survival [32].

We propose a model in which an interplay between abnormal signaling pathways leads from *LMNA* mutations to cardiomyopathy (Figure 1). This model proposes that alterations in A-type lamins, such as those in *Lmna*$^{H222P/H222P}$ mice, lead to activation of ERK1/2 and AKT. One missing piece of the puzzle is exactly how alterations in A-type lamins activate these two signaling pathways. One study has shown that phosphorylated ERK1/2 interacts with lamin A at the inner nuclear membrane [33]. However, it remains unknown how this leads to ERK1/2 activation, especially in striated muscle, when A-type lamins are altered. Regardless of the mechanism behind ERK1/2 and AKT activation in striated muscle, these protein kinases activate mTORC1 signaling, depressing autophagy, which contributes to disease pathogenesis. ERK1/2 also synergizes with TGF-β to induce fibrosis in the heart. ERK1/2, mTORC1 and TGF-β signaling have all been blocked with small-molecule inhibitors in *Lmna*$^{H222P/H222P}$ mice and all of these interventions have had some beneficial impact. However, reducing signaling of each of these pathways alone in *Lmna*$^{H222P/H222P}$ mice is not definitively curative. Future progress may depend on appropriately reducing the activity of more than one of these pathways simultaneously with combinations of safe and effective drugs.

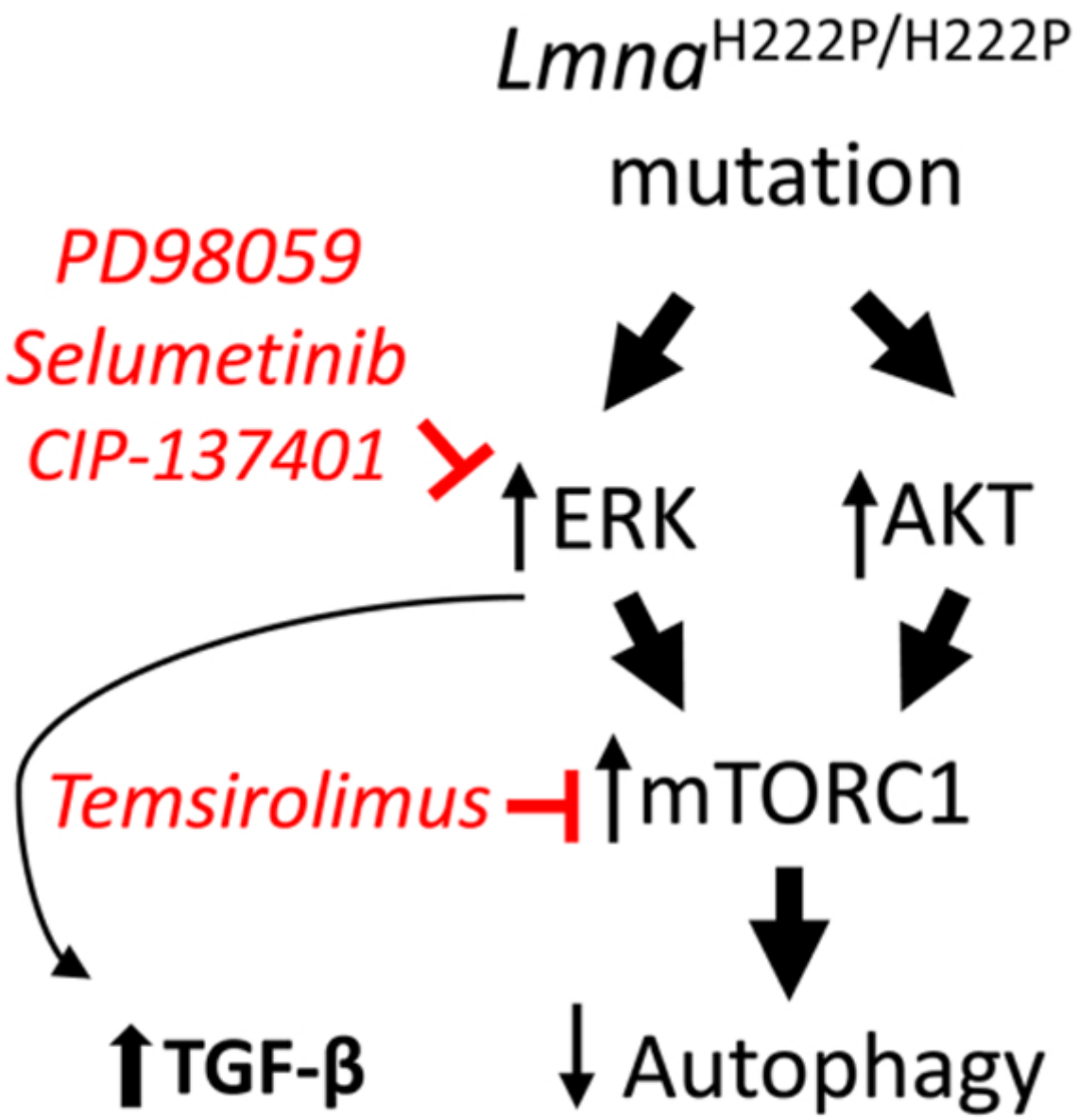

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Figure 1

Model showing interplay between cell signaling pathways leading from *LMNA* mutations to cardiomyopathy.

Most of the data upon which this model is based have come from studies in *Lmna*$^{H222P/H222P}$ mice, a small animal model of 'LMNA cardiomyopathy' in humans. Drugs shown to inhibit each signaling pathway in *Lmna*$^{H222P/H222P}$ mice are shown in red. See the text for a more detailed explanation.

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Competing Interests

H.J.W. has received research support from, is a member of the Scientific Advisory Board of and owns equity in AlloMek Therapeutics, which is developing the MEK1/2 inhibitor CIP-137401. He is also an inventor on a pending patent application related to work discussed in this manuscript.

Abbreviations

AKT	protein kinase B
autophagy	macroautophagy
ERK1/2	extracellular signal-regulated kinases 1 and 2
JNK	c-Jun N-terminal kinase
LMNA	human lamin A/C gene
Lmna	mouse lamin A/C gene
MAP kinase	mitogen-activated protein kinase
MEK1/2	mitogen-activated protein kinase kinases 1 and 2
mTOR	mammalian target of rapamycin
mTORC1	mammalian target of rapamycin complex 1
TGF-β	transforming growth factor-β

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