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Cardiomyopathy Caused by Mutations in Nuclear A-Type Lamin Gene

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<http://dx.doi.org/10.5772/65315>

Abstract

Heart disease is a major cause of morbidity and premature mortality. Cardiomyopathy is an anatomic and pathologic condition associated with muscle and electrical dysfunction of the heart, often leading to heart failure-related disability. Dilated cardiomyopathy caused by mutations in A-type lamin gene (i.e., *LMNA* cardiomyopathy) is characterized by an increase in both myocardial mass and volume. The ventricular walls become thin and stretched, compromising cardiac contractility and ultimately resulting in poor left ventricular function. Despite current strategies to aggressively manage “*LMNA* cardiomyopathy,” the disorder remains a common cause of heart failure with decreased ejection fraction, and a prevalent diagnosis in individuals is referred for cardiac transplantation. Despite progress in reducing “*LMNA* cardiomyopathy”-related mortality, hospitalizations remain very frequent and rates of readmission continue to rise. It appears important and necessary to further increase our knowledge on the pathophysiology of “*LMNA* cardiomyopathy” to unveil novel molecular/cellular mechanisms to target future therapeutic approaches.

Keywords: Dilated cardiomyopathy, Genetics, *LMNA*, A-type lamins, Nuclear lamina

1. Introduction

Cardiomyopathy, a major cause of morbidity and premature mortality in developed countries, is an anatomic and pathologic condition associated with muscle and electrical dysfunction of the heart, often leading to heart failure-related disability, which is a staggering clinical and public health problem. The mechanical component of the heart is liable for pumping blood throughout the body. The electric component, as for it, produces a rhythm for the blood to be pumped correctly. Hence, both components are tightly connected and regulated. Most common symptoms of dilated cardiomyopathy are shortness of breath, leg swelling, decreased exercise tolerance, fatigue, dizziness, coughing or wheezing, weight gain, and palpitation. Given the diversity in severity of symptoms in dilated cardiomyopathy, the disease is not

always diagnosed. Cardiomyopathies are a clinically heterogeneous group of cardiac muscle disorders [1]. Cardiomyopathies have historically been broken down into several major phenotypic categories. Dilated cardiomyopathy, the most common form, is a condition where the heart muscle becomes enlarged and weakened, resulting in poor left ventricular function. Despite current strategies to aggressively manage dilated cardiomyopathy, the disorder remains a common cause of heart failure with a decrease below 45% of ejection fraction and a referring for cardiac transplantation. Notwithstanding progress in reducing heart failure-related mortality, hospitalizations for heart failure remain very frequent and rates of readmissions continue to rise. It appears important and necessary to increase our knowledge on the pathophysiology of cardiomyopathies to unveil novel molecular/cellular mechanisms for future therapeutic approaches.

2. Inherited cardiomyopathies

While the most common cardiomyopathies are secondary to acquired conditions, many are inherited. Genetic mutations have been identified in 25–35% of patients presenting dilated cardiomyopathy. These mutations affect genes that encode components of a wide variety of cellular compartments and pathways, including the nuclear envelope (e.g., *LMNA*, *EMD*), the contractile apparatus (e.g., *MYH7*, *ACTC1*, *TPM1*, *TTN*), the force transduction apparatus (e.g., *MLP*, *DES*, *TNNT2*), and calcium handling (e.g., *SERCA*). The cardiac cell is composed of a complex network of proteins linking the sarcomere to the sarcolemma and the extracellular matrix, providing structural support for subcellular structures and transmitting mechanical signals within and between cells (**Figure 1**). Mutations in genes encoding proteins of the sarcolemma are disrupting the anchoring and hence abrogate the transmission of the force

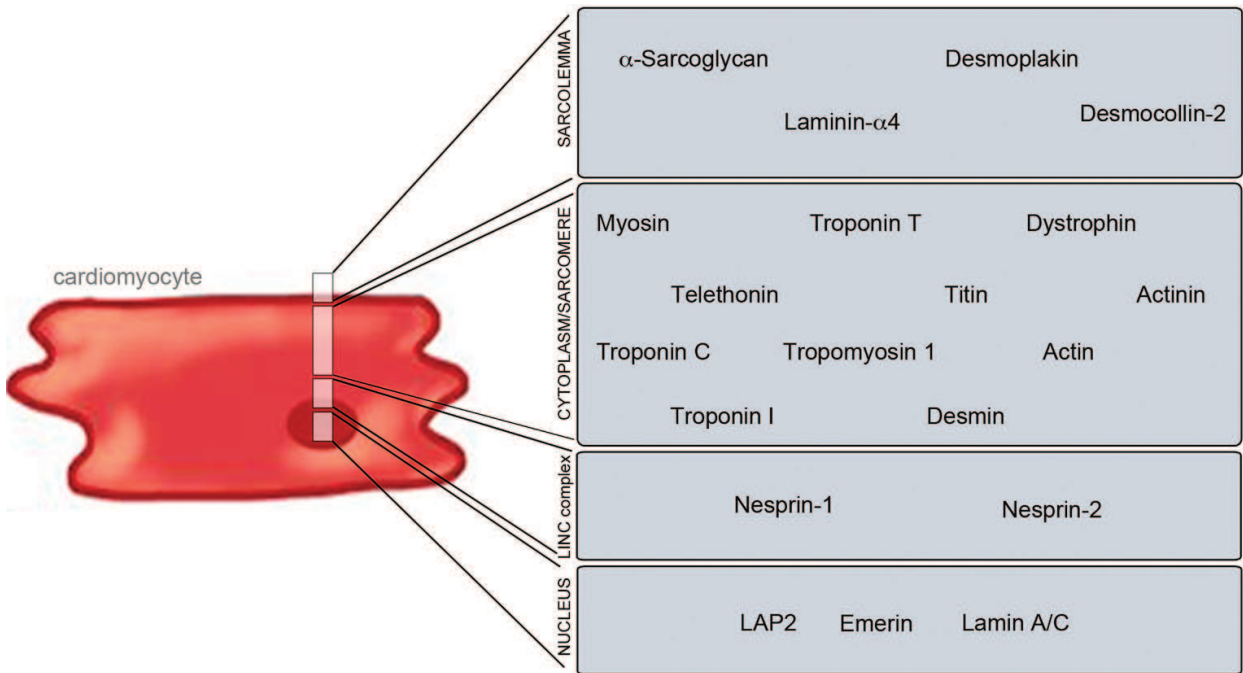


Figure 1. Cellular localizations of proteins involved in dilated cardiomyopathies.

generated by muscle contraction. Muscle contraction is due to the interaction between an actin filament and myosin heavy chain. Mutations in genes encoding contractile elements were identified as the cause of dilated cardiomyopathy. Functional units of striated muscle are called sarcomeres. Because the generated power of muscle contraction is transmitted to adjacent sarcomeres through the Z-disk, mutations in genes encoding proteins of the Z-disk causes also dilated cardiomyopathy. Part of hereditary dilated cardiomyopathies is caused by mutations in the genes encoding proteins of the nuclear envelope. Hence, disruption of the links from the sarcolemma to the sarcomere and nucleus could have a “domino effect,” which leads to the disruption of systolic function and to the development of dilated cardiomyopathy.

3. LMNA cardiomyopathy

Among the causing genes of dilated cardiomyopathy, it has been estimated that mutations in *LMNA*, encoding nuclear lamin A/C [2], accounts for about 5–10% of familial dilated cardiomyopathy, thus representing one of the major causative genes. Affected patients often exhibit early conduction defects before left ventricle dysfunction and dilatation occur [3]. “*LMNA* cardiomyopathy” usually presents in early to mid-adulthood with symptomatic conduction system disease or arrhythmias or with symptomatic dilated cardiomyopathy (**Figure 2A**). “*LMNA* cardiomyopathy” has an intrusive clinical progression with higher rates of aggressive arrhythmias and faster course toward heart failure than most other cardiac diseases. Given the increased awareness among physicians, cardiologists are now facing difficult queries regarding patient management. These queries concern the use of defibrillators in order to avoid sudden death from aggressive ventricular arrhythmias and pharmacological interventions to improve heart failure symptoms. Once dilated cardiomyopathy is detected clinically, the management for “*LMNA* cardiomyopathy” follows the standard of care for heart failure. It is unclear whether early institution of these therapeutic agents prior to detectable cardiac dysfunction can modify the aggressive nature of “*LMNA* cardiomyopathy.” There is no definitive treatment for the progressive cardiac dilatation and loss of contractility in “*LMNA* cardiomyopathy” short of heart transplantation [4].

4. A-type nuclear lamins

The *LMNA* gene, on chromosome 1q21.2-21.3, encodes nuclear A-type lamins. Lamin A and lamin C, the major somatic A-type lamins, arise via alternative splicing of pre-mRNA [5] (**Figure 3A**). Lamin A is primarily synthesized as a precursor, the prelamin A. Prelamin A has a particular C-terminal amino acid tail, which undergoes several enzymatic reactions to produce mature lamin A. Two other genes, *LMNB1* and *LMNB2*, encode lamins B1 and B2, respectively. Lamins are class V intermediate filament proteins that polymerize to form the nuclear lamina (**Figure 3B**), a fibrous network underlining the inner nuclear membrane of most eukaryotic cells (**Figure 3C**) [6–8]. The nuclear lamina is bounded to the inner nuclear membrane via interactions with integral proteins and to the chromatin. It has also been shown that lamin A/C can also interact with the cytoskeleton, through the linker of nucleoskeleton and cytoskeleton (“LINC”) complex [9]. One function of the lamina is to provide structural

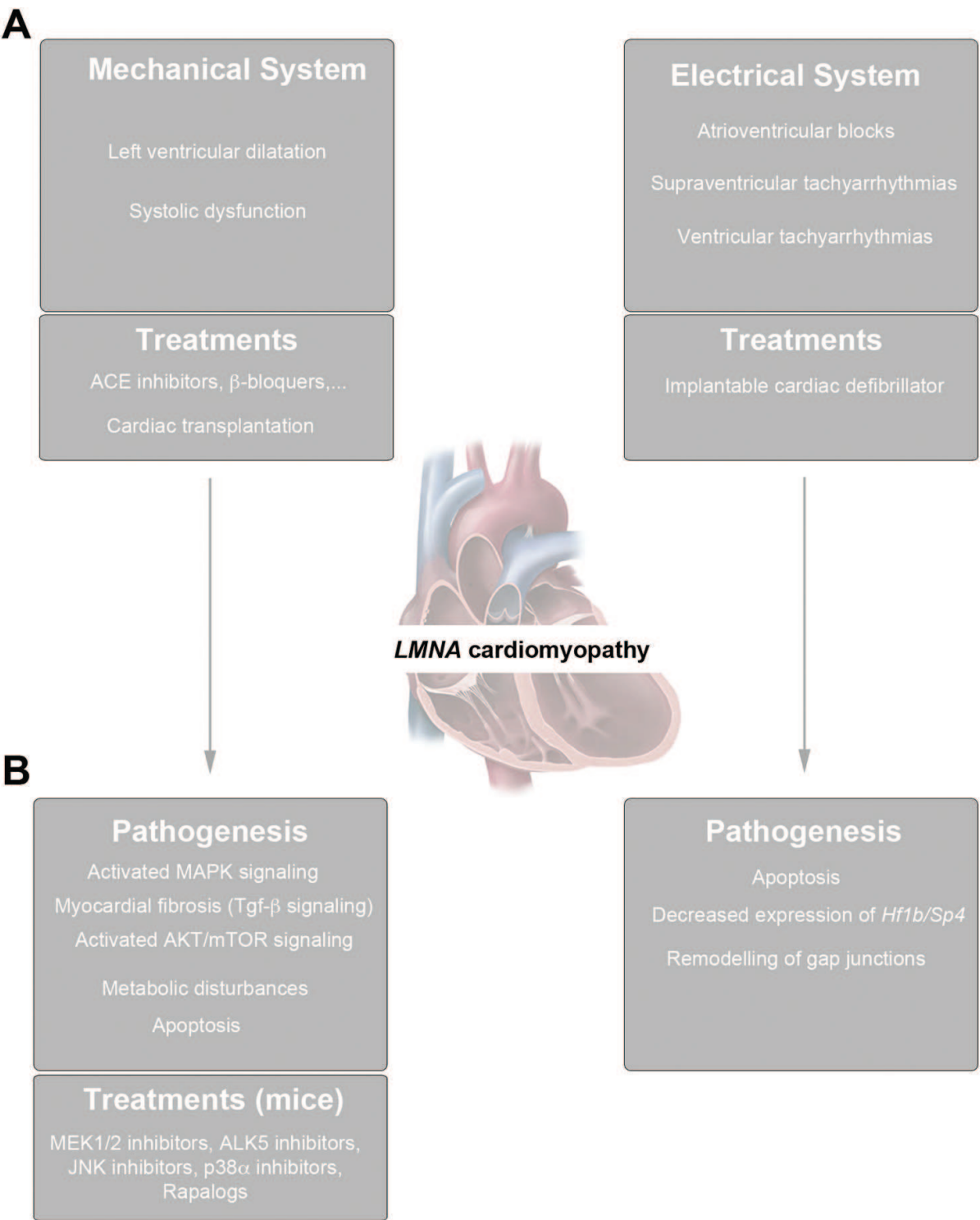


Figure 2. Cardiac symptoms of “LMNA cardiomyopathy (A) and pathological mechanisms (B).

support to the nucleus. Nuclear lamins have also been implicated in processes such as chromatin organization, gene regulation, DNA replication, and RNA splicing [10]. However, the specific mechanistic roles of lamins in these processes, particularly in a cell- or tissue-type-specific context, remain obscure.

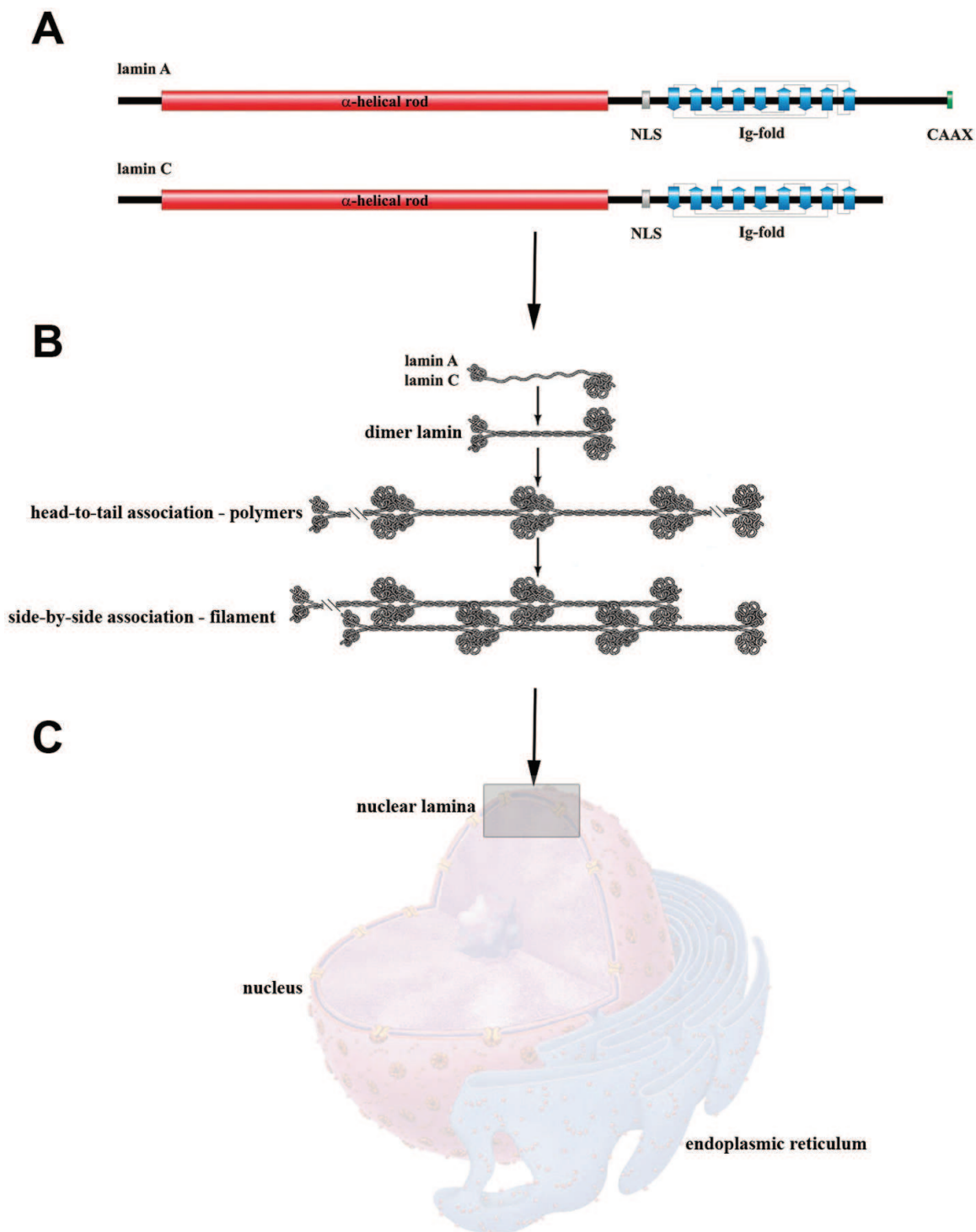


Figure 3. Nuclear lamins: structure (A), organization (B), and cellular localization (C). Modified from [10].

5. Pathogenesis

Identification of disease-causing mutations in the heart has contributed to the delineation of “LMNA cardiomyopathy.” However, much work remains in elucidating the specific cellular mechanisms of the disease. Several hypotheses have been proposed attempting to link the

pathophysiology of “LMNA cardiomyopathy” to known or emerging functions of lamin A/C. Among these functions include those based on that lamin A/C likely have in maintaining the mechanical integrity of cells subject to external and internal cues and signal transduction (i.e., the mechanical stress hypothesis). The “mechanical stress hypothesis” is attractive when trying to explain striated muscle diseases. It is based on the premise that the striated muscles are constantly subjected to mechanical forces and that mutations in “nucleocytoskeletal” support elements make them susceptible to damage from recurrent stress. Mouse models have been extremely helpful in deciphering crucial mechanisms, which could partially explain the pathogenesis of the disease. The development of *Lmna*^{−/−} mice by Sullivan and colleagues was the first animal model of the disease [11]. Since, other models (knock-in and transgenic) have been created to study the cardiac dysfunction caused by LMNA mutation [12–15]. We and others reported an aberrant cardiac activation of signaling pathways in “LMNA cardiomyopathy” [16, 17] in mice and human, which participate to the development of contractile dysfunction (mitogen-activated protein kinase (MAPK) signaling, AKT/mTOR signaling, TGF- β signaling, etc.) [16, 18, 19] and electrical disturbances (connexin 43 remodeling, apoptosis, Hflb expression) (**Figure 2B**).

MAPK signaling—One of the most prevalent and best-characterized responses to mechanical stress is the phosphorylation of proteins, which could be mediated by mitogen-activated protein kinase (MAPK) signaling pathway. Genes encoding proteins in MAPK signaling pathway demonstrated significantly altered expression in hearts of *Lmna* H222P mice by transcriptomic analysis [16]. We demonstrated an aberrant activation of ERK1/2, JNK, and p38 α signaling, three main branches of MAPK signaling pathway involved in cellular mechanotransduction, in hearts from *Lmna* H222P mice, as early as 4 weeks of age [16, 17]. Our work proved that the activation of MAPK signaling pathway preceded the cardiac dysfunction of *Lmna* H222P mice and that it is a consequence of alterations in lamin A/C and not secondary to nonspecific effects. Accordingly, lamin A/C-deficient fibroblasts subjected to cyclic strain respond with decreased expression of the mechanosensitive genes, which are downstream targets of the MAPK pathway [20].

AKT/mTOR signaling—We showed that the *Lmna* pH222P mutation results in aberrant activation of the AKT/mTOR signaling cascade, downstream of the MAPK pathway [18]. Given that activated mTOR inhibits autophagic responses and reduces tolerance to energy deficits, the heart is therefore unable to compensate for increased energy demand and, over time, develops muscle damage and dilated cardiomyopathy.

TGF- β signaling—Cardiac fibrosis exacerbates the clinical progression of heart failure. We showed that *Lmna* H222P mice had elevated expression of TGF- β signaling as early as 12 weeks of age, which is a time that preceded development of both cardiac fibrosis and the onset of overt cardiac dysfunction [13, 19]. Our observations indicate that TGF- β is a mediator of the cardiomyopathy that develops as a result of LMNA mutations.

Connexin 43 remodeling—Gap junction communications describe the electrical coupling of cells through specialized cell contacts called gap junctions. In adult heart, connexin 43 is expressed in the atrial and ventricular working (contractile) myocardium. The working cardiomyocytes of the ventricle are extensively interconnected by clusters of connexin 43 located at the

intercalated disks. The intercalated disks of working ventricular myocardium have a step-like configuration, with the gap junctions situated predominantly in the “horizontal” facing segments of these steps rather than the vertical segments [21, 22]. Features of gap junction organization encourage preferential propagation of the impulse in the longitudinal axis, thus contributing to the normal pattern of anisotropic spread of the impulse of healthy ventricular myocardium. The most striking form of structural remodeling connexin 43 is typically scattered in disordered fashion over the lateral surfaces in the heart from *Lmna* N195K mice (i.e., lateralization) [12].

Apoptosis—Apoptosis in all metazoan cells is mediated by caspases, a multigene family of cysteine proteases that hydrolyzes peptide bonds carboxyl to aspartic acid residues. Once activated, caspases cut cellular proteins, leading to the apoptotic demise of the cell. During the past few years, there has been accumulating evidence in both human and animal models suggesting that apoptosis may be an important mode of cell death during heart failure [23]. Myocyte apoptosis has been reported in the atrioventricular tissue from *Lmna*^{+/-} mice [24], which could account for the evolution of electrophysiologic dysfunction.

Hf1b/Sp4—This transcription factor has been described as important for the development of the cardiac conduction system [25]. Mounkes and colleagues found that expression and localization of Hf1b/Sp4 were altered in the heart from *Lmna* N195K mice [12]. Strikingly, this study reported that Hf1b/Sp4 was not found in the ventricles and was strongly expressed in the atria in the heart from *Lmna* N195K mice, which mirror the localization in control animals. This finding needs further analysis.

The exact mechanisms by which defects in nuclear lamins cause dysregulated signaling remain to be elucidated.

6. Treatments

Advances in molecular techniques have improved the understanding of mechanisms responsible for cardiac dysfunction in “LMNA cardiomyopathy.” It is clear that mutations in nuclear lamin A/C in cardiomyocytes can perturb cardiac function. Alterations in cardiomyocyte function initiate cascades of cellular responses that attempt to compensate for these insults. However, persistent responses at the cellular level lead to organ-wide alterations, which correlated with sudden cardiac death and heart failure. Although there exists no treatment to directly address the causes of “LMNA cardiomyopathy,” basic studies of the processes that mediate cellular responses to cardiac stress have allowed the development of innovative treatments that address the reduction of symptoms that include drugs that decrease blood pressure (ACE inhibitors, angiotensin II receptor blockers, beta-blockers) and heart rate (beta-blockers, calcium channel blockers, digoxin) to reduce the strain on the ventricular walls. Utilization of animal and cellular models to further dissect the mechanisms of “LMNA cardiomyopathy” and demonstrate efficacy of drugs that specifically target disease-causing pathways holds promise that further reduction in the mortality associated with “LMNA cardiomyopathy” can be achieved [17–19, 26, 27].

7. Conclusion

In the past decade, there has been an extraordinary burst of researches on lamin A/C and the nuclear lamina, which has been accelerated by attempts to explain the pathogenesis of “LMNA cardiomyopathy.” One important unanswered question is how mutations in genes expressed in most differentiated somatic cells lead to human disease affecting the cardiac tissue. Within the next several years, we will likely have more clues to answer this question, and these answers will hopefully lead to new ways to treat or prevent “LMNA cardiomyopathy.”

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