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Chapter

Animal Models of Cardiomyopathies

Enkhsaikhan Purevjav

Abstract

Cardiomyopathies are a heterogeneous group of disorders of heart muscle that ultimately result in congestive heart failure (CHF). Rapid progress in genetics as well as in molecular and cellular biology over the past three decades has greatly improved the understanding of pathogenic signaling pathways in inherited cardiomyopathies. This chapter will focus on animal models of different clinical forms of human cardiomyopathies with their summaries of triggered key molecules, and signaling pathways will be described.

Keywords: cardiomyopathy, heart failure, genetic mutation

1. From genetic abnormality to cardiomyopathy phenotype

It's widely accepted that inherited cardiomyopathies are a group of heterogeneous diseases of heart muscle resulting from genetic alterations in cardiac myocytes, the chief contractile cell type in the heart [1]. The genes encoding proteins that build muscle cytoskeleton and contractile apparatus are responsible for a cardiomyopathy phenotype with distinctive morpho-/histological cardiac remodeling [2]. Further, disruption of particular genetic and protein networks and pathways may intersect with other intracellular and intercellular pathways and disturbances in molecular signaling. Apoptosis, necrosis, autophagy, and metabolic and arrhythmogenic fluxes—which may present as the sole features or as overlapping signs of decompensated cardiac homeostasis—result in definitive forms of cardiac remodeling including fibrosis, cardiomyocyte hypertrophy, and atrophy. Typically, molecular signaling activates associated compensatory responses and cooperates with other modifiers such as genetic modifiers and environment, stress, or toxicity related that, in turn, may or may not influence the final cardiomyopathy phenotype. Alterations in cellular morphology and size, gene expression patterns, and metabolic shifts in cardiomyocytes initially compensate and maintain cardiac function in the subtle, preclinical stages of cardiomyopathy. Thus, inherited forms of cardiomyopathy, irrespective of the specific genetic or morpho-/clinical condition, may or may not present signs of a failing heart. Five types of inherited cardiomyopathies are distinguished based on clinical features: dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), arrhythmogenic ventricular cardiomyopathies (ACM), and left ventricular noncompaction cardiomyopathy (LVNC) [3] as demonstrated in Table 1. DCM is characterized by left ventricular (LV) dilation and systolic dysfunction; HCM is characterized by LV hypertrophy with diastolic dysfunction; and RCM is accompanied by increased stiffness of the myocardium and dilated atria due to
diastolic dysfunction without significant hypertrophy [4]. Frequent and often life-threatening arrhythmias and associated sudden cardiac death and progressive heart failure are the main hallmarks of ACMs [5], while myocardial hypertrabeculation, intertrabecular recesses, and thin compact LV wall are the characteristics of LVNC [6]. Sustained maladaptive remodeling due to pathologic genetic insult results in the development of decompensated cardiomyopathy when the failing heart is unable to keep up with the hemodynamic demands at all levels, from the molecule to the whole organism. When compensatory mechanisms fail, additional neuroendocrine signaling and other pathways are activated on an organ and whole organism level, leading to CHF. Cellular and molecular level alterations of end-stage cardiomyopathy and CHF respond to irreversible cardiac remodeling with significant changes in membrane ion currents and intracellular Ca$^{2+}$ metabolism, fibrosis, hypertrophic or atrophic remodeling, and cell death. Cardiac function is significantly depressed with depleted contractile force development and slowed relaxation [7].

2. Animal models of human cardiomyopathies

Translational comparative animal research is of considerable value in inherited cardiomyopathies, because animal models enable to explore and investigate the cellular and molecular pathology originating from the initial genetic assault but also may closely recapitulate the effects of cardiac remodeling culminating into a specific cardiomyopathy type seen in humans. Animal models carrying human gene mutations may not present clinical phenotypic signs of cardiomyopathy resembling the human disease until adulthood, supporting a temporal mechanism by which chronically altered cellular responses and cardiac remodeling lead to the clinically relevant phenotype.

2.1 Naturally occurring animal models of cardiomyopathy

Naturally occurring cardiomyopathy among small and large animals is commonly observed in canine and feline species [8, 9]. HCM is a common disease in pet
cats, affecting 10–15% of the pet cat population [10], while DCM is more typical in
dogs [11]. The similarity to human HCM or DCM, the rapid progression of disease,
and the defined and readily determined endpoints of feline HCM or in canine DCM
make them excellent natural models that are genotypically and phenotypically
similar to human heart muscle disease [12]. The Maine Coon and Ragdoll cats are
particularly valuable models of HCM associated with myosin binding protein C
(MyBP-C) mutations and even higher disease incidence compared to the overall
feline population [13, 14]. In canine, mutations in genes such as dystrophin (DYST)
in German Shorthaired Pointers [15], desmin (DES) and α-actinin in the Doberman
[16, 17], titin-cap (TCAP) in Irish Wolfhounds [18], and striatin in Boxers [19] were
reported to be associated with DCM. In addition, many naturally occurring porcine
HCM and DCM have been described offering the useful models for translational
research [20–22].

2.2 Genetically engineered animal models of cardiomyopathy

Experimentally, numerous small and large animal models including fruit fly,
fish, rodents, rabbit, canine, pig, and other species have been developed to discover
pathogenetic mechanisms involved in cardiomyopathy in the research field [23–25].
Characterization of the mechanisms of cardiomyopathies using the study of animal
models is challenging owing to the complexity of disease-causing mechanisms and
modulators of pathology [25]. Moreover, animal models are successfully used for
genome-wide screening, assessing of cardiac phenotypes and disease symptoms,
genotype-phenotype association studies, and drug discovery and development
assays. The accessibility of transgenic (TG), knockout (KO) and knock-in (KI)
murine models has, however, been one of the most successful approaches for
studying genetic cardiomyopathies [26]. With recent advances in CRISPR/Cas9
technology, researchers are able to achieve more effective and precise genome edit-
ing because of its simplicity, design, and efficiency over other traditional methods
for genetic editing such as transgenesis and homologous recombination targeting
methods [27–29].

The lowest species that has typically been used for cardiomyopathy research is
Drosophila melanogaster as a tool to study various developmental biological processes
and mechanisms underlying congenital defects and inherited heart diseases [30, 31].
The Drosophila heart looks as a primitive linear tube similar to embryonic heart tube
in vertebrates, and many heart development, function, and aging regulatory genes
and networks such as NK-2, MEF2, GATA, Tbx, and Hand have been evolutionarily
conserved. The conserved development of the heart in simple model organisms
and vertebrates provides a unique ability to use many different animal models in
cardiomyopathy research [32]. Important advantages of the use of animal models
are the ability to manipulate gene expression and identify genes and mechanisms
regulating heart development, cardiac pathology, and pathophysiology [33, 34].
Advanced systems to identify genes causing human cardiomyopathies such as UAS/
GAL4 [35], techniques for accurate phenotyping of cardiac diseases such as optical
coherence tomography [36], powerful electrophysiological, mechanical, and
histological approaches to characterize heart development, cardiac tissue properties,
and structure in the Drosophila heart have emerged as a pioneering model system in
basic, genetic, and molecular studies of cardiac development, function, aging, and
disease [37]. Numerous Drosophila models have been used to elucidate the patho-
physiology of human HCM and DCM and other heart diseases, such as heart failure,
cardiac tachycardia, atrial fibrillation, and congenital heart diseases [38–40].

The zebra fish (Danio rerio) model remains one of the most effective technolo-
gies for discovering and functional studying novel cardiomyopathy candidate
genes, especially the ability to use morpholino knockdown techniques in fish models [26, 41, 42]. Compared with other vertebrate models, the zebra fish embryos are transparent allowing genetic engineering approaches to apply fluorescent reporter transgenes with genetic fate mapping strategies combined with high-resolution, high-throughput microscopy imaging in vivo of the heart [43, 44]. The transparency of the embryos allows to observe fluorescent proteins that are expressed in various cell types of the cardiovascular system, and these research advances have opened avenues to improve our knowledge of regulatory mechanisms of cardiomyocyte and other cardiac cells’ differentiation [45, 46], regeneration [44], morphogenesis [47], drug effects and toxicity [48], and gene regulation [49]. The advancement in high-speed video imaging and automated image analysis techniques including light sheet planar illumination microscopy not only allows to precisely monitor morphologic and functional characteristics such as heart rate, arrhythmias, and ejection fraction in zebrafish but also progresses our current understanding of the different types of cardiomyopathy.

Rodent models are the most used model species for cardiomyopathy research, including genetics, pharmacology, and long-term survival considering that rodents have a short gestation time, have the ability to be genetically manipulated to generate transgenic or mutant strains, and are easy to handle and house with low maintenance costs [24, 50]. In addition, a fact that mice have short life span allows investigators to generate genetic models in a shorter time period and follow the natural history of genetic diseases at an accelerated pace, enabling to rapidly launch proof-of-principle experiments and potentially translating and exploiting the results into human studies. Significant advantages to rodents as the species of choice can limit the murine data’s applicability to human cardiovascular function; there are significant differences between the mouse models and human disease presentation [25]. Rodents are phylogenetically farthest distant from humans compared to other mammals, and some pathophysiological features of cardiomyopathy phenotypes and their response to environmental stress and treatments may not be reliable for human diseases [23].

The rabbit and pig experimental models of cardiomyopathy offer significant advantages for cardiovascular research [50]. Compared with the mouse, the larger size and slower heart rate of the rabbit and pigs are advantageous for physiological analyses such as echocardiography and cardiac catheterization.

2.2.1 Hypertrophic cardiomyopathy animal models

Animal models of HCM mostly carry human mutations in sarcomeric protein-encoding genes such as α-MHC, α-tropomyosin, troponins, myosin binding protein C (MyBP-C), and other genes shown in Table 1 [51–55]. Many models carry cardiac-specific (CS) expression or ablation of the proteins of interest. These models have demonstrated that HCM mutations enhance contractile properties with increased force generation, ATP hydrolysis, and actin-myosin sliding velocity, showing that the hypertrophy is not a compensatory response to diminished contractile function [56–58]. Models of HCM also show abnormal Ca²⁺ cycling in cardiomyocytes before overt histopathologic changes occurred in the myocardium and delayed myocardial relaxation that occurs before the onset of hypertrophy, suggesting that diastolic dysfunction is a direct consequence of HCM mutations [59, 60]. Hearts from models of HCM progressively accumulate myocardial fibrosis in the same manner as human patients, and fibrosis is considered to be a cellular substrate for cardiac arrhythmias and sudden cardiac death in humans [61–63].
2.2.2 Dilated cardiomyopathy animal models

Animal models of DCM mostly resemble human mutations in genes encoding cytoskeletal, sarcomeric, and Z-disk proteins and present with ventricular dilation and thinning of the ventricular walls correlated with loss of heart muscle mass. In addition, functional changes in non-myocytes induce fibrotic scars that

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<td>α-MHC</td>
<td>HCM</td>
<td>murine TG R10Q [33]</td>
<td>HCM</td>
<td>myocyte disarray, fibrosis, atrial dilation</td>
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<td>Cavolin3</td>
<td>HCM</td>
<td>murine KO [22]</td>
<td>HCM, DCM, cardiac dysfunction</td>
<td>ERK1/2 activation, Src signaling</td>
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<td>Cavolin3</td>
<td>HCM</td>
<td>murine TG P104L [33]</td>
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<td>nNOS production, altered endoplasmic reticulum (ER) stress response</td>
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<td>Cavolin3</td>
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<td>Titin</td>
<td>HCM</td>
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<td>HCM, fibrosis and atrial enlargement</td>
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Table 2. Animal models of hypertrophic cardiomyopathy.
stiffen the heart tissue and impede normal cardiomyocyte contractility. Novel DCM mechanisms such as impaired Z-disk assembly, sensitivity to apoptosis and abnormalities in myofibrillogenesis under metabolic stress, protein folding, inhibition of protein aggregation, and degradation of misfolded proteins have been explored (Table 2).

![Table 3. Animal models of dilated cardiomyopathy.](image-url)
2.2.3 Restrictive cardiomyopathy animal models

RCM is the least common but most lethal form of cardiomyopathy where impaired ventricular relaxation due to increased stiffness of the myocardium and pressure in the ventricles overcomes the changes in myofibrillar arrangement and cardiomyocyte gross abnormalities [113]. Animal models carrying human RCM-associated mutations have also been generated to mimic human RCM phenotype. These mutations are identified mainly in sarcomeric protein-encoding genes such as troponins, myosin and MYPN (summarized in Table 3).

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<td>Mls</td>
<td>murine KO</td>
<td>RCM</td>
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Table 4.
Animal models of restrictive cardiomyopathy.
2.2.4 Arrhythmogenic ventricular cardiomyopathy models

Many models of ARVC with mutations in genes encoding desmosomal (DSP, PKP, DSC, DSG, and JUP) and non-desmosomal (RYR2, TMEM43, and ZASP) proteins have been developed [118]. Structural and functional alterations include progressive, diffuse, or segmental loss of cardiomyocytes, probably due to cardiomyocyte apoptosis or necrosis, and replacement with fibrotic and adipose tissue (Table 4). Fibro-fatty tissue primarily is seen in the right ventricle (RV), with common LV involvement in later stages of the disease [119] (Table 5).

2.2.5 Left ventricular noncompaction cardiomyopathy models

Animal models of LVNC typically demonstrate a spongiform ventricular myocardium and deep trabeculations, and many reports suggested that LV trabeculation and compaction processes are two distinct but tightly interconnected morphogenetic events resulting in the development of a functionally proficient ventricular chamber wall [140]. Animal models exhibiting LVNC phenotypes and potential pathogenetic mechanisms are summarized in Table 6.

3. Conclusion

Advances in molecular and genetic techniques have vastly improved the understanding of molecular mechanisms responsible for cardiomyopathies and cardiac
dysfunction. The wide range of innovative technologies and techniques used in animal models in vivo has led to advances in our knowledge on the etiology, pathophysiology, and therapeutics of inherited cardiomyopathies. It is clear that mutant proteins in cardiomyocytes can perturb cardiac function whether the prime distress occurs in the contractile apparatus or neighboring cellular complexes, yet persistent cellular stress leads to tissue-, organ-, and organism-level pathology and pathophysiology. However, development and investigation of animal models are complex processes and the outcomes of which could be difficult to translate to humans due to differences in human and animal cardiovascular anatomy and physiology as well as differing pathophysiology of human cardiomyopathies and experimentally induced diseases in animals [160]. Therefore, the choice of appropriate animal model(s) for cardiomyopathy research should utterly rely on clinical knowledge of human cardiovascular diseases, proper research questions, sufficient number of study animals, and correct and relevant interpretation of results and outcomes in animals to human population. Although animal models of human cardiomyopathies often represent incomplete or inaccurate pathological and pathophysiological features seen in humans, the use of animal models not only has improved our knowledge on the etiology and mechanisms of cardiac muscle diseases and therapeutic interventions but also has greatly promoted an advancement in cardiac tissue engineering, induced pluripotent stem cells (iPSCs) technology, in silico and in vitro techniques, and preclinical assessment of drug discovery and development [161].

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